RISK FACTORS FOR CHILDHOOD REFRACTORY EPILEPSY IN A TERTIARY CARE CENTRE, CHENNAI

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In partial fulfillment of the regulations for the award of degree of

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(BRANCH VII)

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN

MADRAS MEDICAL COLLEGE

CHENNAI

APRIL - 2016

CERTIFICATE

This is to certify that the dissertation titled **"RISK FACTORS FOR CHILDHOOD REFRACTORY EPILEPSY IN A TERTIARY CARE CENTRE, CHENNAI"** submitted by **Dr.G.Thannoli Gowthami** to the Faculty of Paediatrics, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (Paediatrics) is a bonafide research work carried out by under our direct supervision and guidance.

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I Dr.G.Thannoli Gowthami solemnly declare that the dissertation titled **"RISK FACTORS FOR CHILDHOOD REFRACTORY EPILEPSY IN A TERTIARY CARE CENTRE", CHENNAI** has been prepared by me.

This is submitted to The **Tamilnadu Dr.M.G.R. Medical University,** Chennai in partial fulfillment of rules and regulations for the **M.D.Degree** Examinations in **Paediatrics**.

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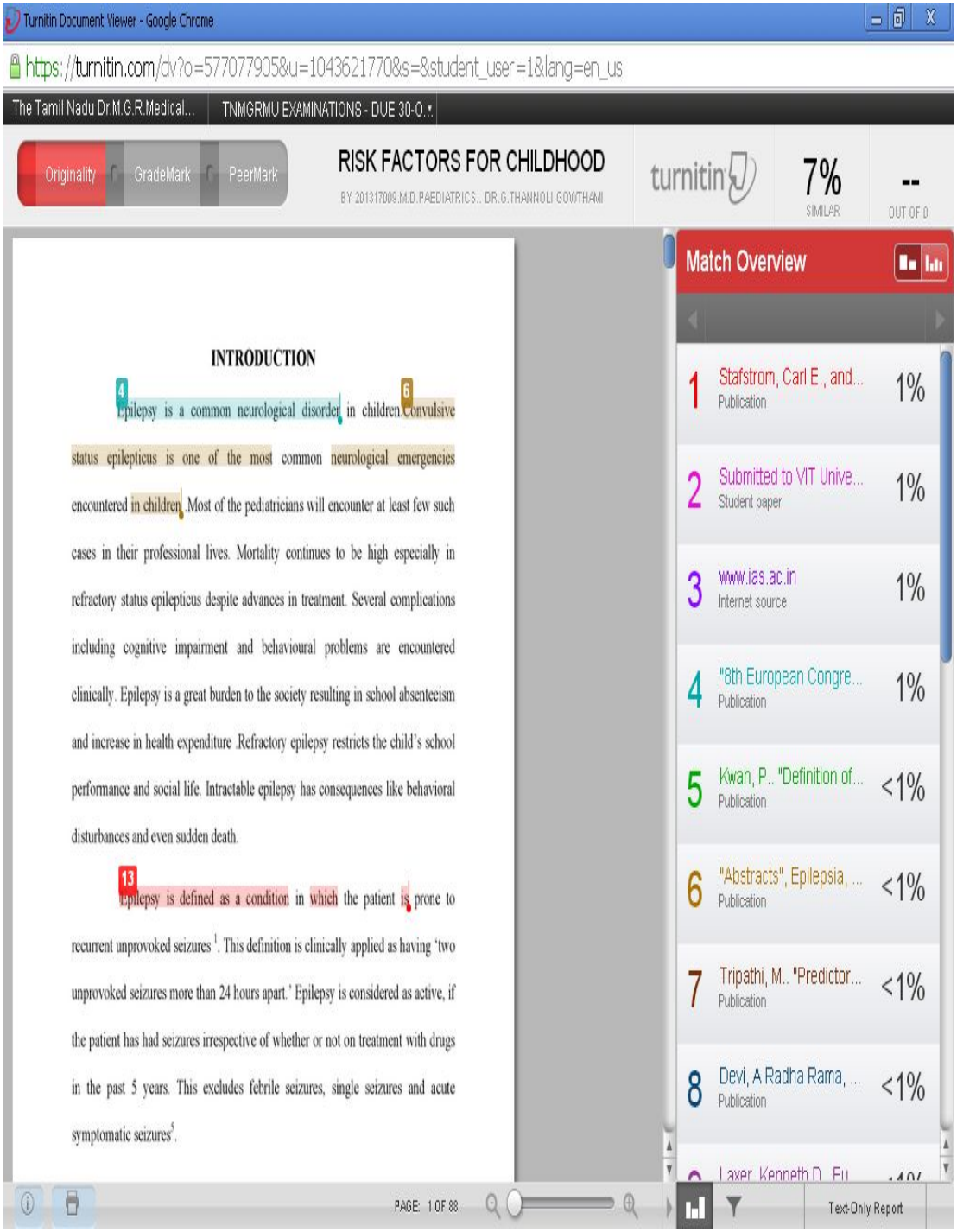
CONTENTS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INTRODUCTION
Epilepsy is a common neurological disorder in children.Convulsive status epilepticus is one of the most common neurological emergencies encountered in children .Most of the pediatricians will encounter at least few such cases in their professional lives. Mortality continues to be high especially in refractory status epilepticus despite advances in treatment. Several complications including cognitive impairment and behavioural problems are encountered clinically. Epilepsy is a great burden to the society resulting in school absenteeism and increase in health expenditure .Refractory epilepsy restricts the child's school performance and social life. Intractable epilepsy has consequences like behavioral disturbances and even sudden death.
Epilepsy is defined as a condition in which the patient is prone to recurrent unprovoked seizures [1]. This definition is clinically applied as having 'two unprovoked seizures more than 24 hours apart.' Epilepsy is considered as active, if the patient has had seizures irrespective of whether or not on treatment with drugs in the past 5 years. This excludes febrile seizures, single seizures and acute symptomatic seizures[5].
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ABSTRACT

AIM

Aim to identify the risk factors of refractory childhood epilepsy.

OBJECTIVES

To identify the association of karyotyping analysis in refractory epilepsy.

To prognosticate the seizures in refractory childhood epilepsy.

MATERIAL AND METHODS

This is a Descriptive study carried out in ICH, the tertiary care centre in Chennai to identify the risk factors of refractory epilepsy. The children of age group 6 months to 12 years with refractory seizures were evaluated with the standard questionnaire, data pertaining to the refractory epilepsy were extracted from the medical records of the patients and analyzed. The patients with idiopathic type of seizures with normal phenotype as well as with dysmorphism were sent for karyotyping to know the association of ring chromosome and inversion chromosome with refractoriness.

STASTICAL ANALYSIS

Chi square test/fisher Exact test were carried out to determine the potential significance (p value less than 0.05)

RESULTS

One hundred fifty two children with refractory epilepsy were evaluated.with results of male sex predominantly affected (104,69.1%). infantile onset of seizures(83,54.6%), generalized seizure(71,46.7%), Myoclonic epilepsy (43,28.3%), Infantile spasms, perinatal injury (64,42.1),neonatal seizures (53,34.9%),developmental delay (107,70%), abnormal EEG

(129,84.9%),abnormal cerebral imaging (106,69.7%)neurological abnormality (100,68%) high seizure score showed a significant association with refractory epilepsy.

CONCLUSION

From this study, the risk factors identified should be evaluated properly a treated appropriately. Early identification helps the parents to be counseled about the need for continuation of the drugs, associated co-morbid conditions and risk involved in recurrent seizures. The parents should be appraised of the child’s condition and help in improving the quality of life.

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Magnitude of epilepsy:

Around 1-2% of the world's population, which is 50 million are affected by epilepsy[2].It is estimated that 80-90% live in developing countries. In the four community based series in North India, Central, South India shows the prevalence of 2.5 per 1000 in Kashmir, 3.6 per 1000 in Mumbai, 4.4 per 1000 in Bangalore, 4.9 per 1000 in Kerala[4]. In India the prevalence is 572.8/100,000. Incidence being 27.27/100,000 and 7.63/100,000.[3]

CLASSIFICATION:

Precise recognition and classification of the epilepsy and seizures is the cornerstone for planning the management.

'SEIZURE' is defined as a transient clinical manifestation resulting from abnormal [excessive and hyper synchronous] neuronal discharge, which is paroxysmal, transient and self limiting.[6]

Etiological approach shows two subgroups in acute seizures,

- Acute symptomatic seizure [ASS] - situation related, provoked seizures and reactive seizures that occur at the time of a systemic injury or association with a documented brain damage. Example: Febrile seizures

- Unprovoked seizures [US]- without any triggering factor except individual susceptibility.

Epilepsy is the liability to have recurrent unprovoked seizures[7].

As per 2010 International league against epilepsy [ILAE] Classification:

Classification of the epileptic seizure is with

1. Seizure type
2. Etiological classification and
3. Electroclinical classification

GENERALIZED SEIZURES;

A. Tonic –clonic.

B .Absence.

Typical

Atypical

Absence with myoclonia, eyelid myoclonia

C. Myoclonic,

Myoclonic tonic

D. Clonic

E.Tonic

F.Atonic

FOCAL SEIZURES

- Simple partial seizures
- Complex partial seizures
- UNKNOWN

  Epileptic spasms.

Epilepsy etiologies-classification of epilepsy and epileptic syndrome as per the 2010 classification[11]

The Epilepsy syndrome by ILAE classification defines an epileptic syndrome as a disorder with cluster of signs and symptoms that customarily occurs with it.

Old concepts and terms	New concepts and terminology
Idiopathic	Genetic;
Symptomatic	Structural
Cryptogenic	Unknown

Genetic: Epilepsy is the direct result of genetic or presumed genetic defects example: Dravet syndrome.

Structural or metabolic: Due to tumor, stroke, trauma, infection, there may be a genetic origin e.g. tuberous sclerosis.

Unknown cause: underlying cause of epilepsy is not known or an unrecognized disorder.

ELECTROCLINICAL SYNDROME:

It is a cluster of electroclinical characteristics.

Clinical entity which includes the age of onset, type of seizure, predictive and triggering factors, neurological examination, pattern of seizure with respect to sleep, EEG features, Physical or mental symptoms ,prognosis, response to treatment ,mode of inheritance are the criteria for diagnosis.

If the epilepsy does not fit in the electro clinical syndrome it can be classified as known etiology or seizure type which is considered with distinctive constellations on the basis of specific lesion or other causes. There are other syndromes which do not fit in the electro clinical syndromes but added up with this for the implications of clinical treatment particularly surgery.

ELECTROCLINICAL SYNDROME AND OTHER EPILEPSIES

CLASSIFICATION:

NEONATAL PERIOD
Benign familial neonatal seizures (BFNS)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome

INFANCY
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile seizures
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders

CHILDHOOD
Febrile seizures plus (FS+) (can start in infancy; this can be with generalized [GEFS+] or with focal seizures)
Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BCECTS)
Late-onset childhood occipital epilepsy (Gastaut type)
Autosomal dominant nocturnal frontal lobe epilepsy (AD-NFLE)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome
Childhood absence epilepsy (CAE)

ADOLESCENCE–ADULT
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies

AGE-RELATED (AGE OF ONSET LESS SPECIFIC)
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies

SEIZURE DISORDERS THAT ARE NOT TRADITIONALLY GIVEN THE DIAGNOSIS OF EPILEPSY
Benign neonatal seizures (BNS)
Febrile seizures (FS)

EPILEPTIC ENCEPHALOPATHIES
EME
Ohtahara syndrome
Migrating partial seizures of infancy
West syndrome
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Epilepsy with myoclonic astatic seizures
Lennox-Gastaut syndrome
Epileptic encephalopathy with CSWS
Landau-Kleffner syndrome

OTHER SECONDARY GENERALIZED EPILEPSIES
Generalized epilepsy secondary to neurodegenerative disease
Progressive myoclonus epilepsies

REFRACTORY EPILEPSY

Definition of Refractory Epilepsy:

"A failure of adequate trials of two tolerated, appropriately chosen and used AED schedule [as monotherapies or combination] to achieve sustained seizure freedom."

ILAE latest definition encompasses two hierarchical levels. This provides a scheme to categorize outcome of the treatment.

Level 1 as 'seizure freedom' (defined as freedom from seizures for minimum three times, the longest pre-intervention or inter seizure interval of 12 months.)

Level 2 as 'treatment failure' (defined as recurrent seizure after intervention has been adequately applied) or 'undetermined' (defined as whether has not been applied adequately for a valid assessment of outcome or adequate information is lacking to make the assessment). Level 1 forms a basis for level 2[8]. This defines the Refractory epilepsy.

Etiology of the refractory Epilepsy

1. Epileptic syndrome - early myoclonic encephalopathy, early infantile epileptic encephalopathy, West syndrome, Lennox Gastaut syndrome (LGS), Rasmussen encephalitis.

2. Brain damage due to perinatal insults, porencephalic cysts, CNS infections
3. Mesial temporal lobe sclerosis
4. Structural brain damage –Neuronal migrational disorder, TSC, Struge Weber syndrome, hemangiomas, brain tumours, neuro degenerative disorder, neuro metabolic disease
5. Early onset of epilepsy in the infancy or less three years of age is a major risk factor
6. Neonatal seizures are the risk factor.
7. Abnormal neurological examination, microcephaly, developmental delays are identified as the major risk factor.
8. Abnormal EEG findings
9. Increased seizure frequency prior to treatment,
10. Symptomatic epilepsy.
11. H/O febrile convulsions, H/O presentation with status epilepticus, Family history of epilepsy is variably associated.

Complication of the refractory Epilepsy:

Mortality: The children with refractory Epilepsy have increased mortality rate. Children with neurodegenerative disorder, status epilepticus are more prone to early mortality.

Morbidity: Refractory seizures leads to increased co-morbid conditions like behavioral, cognitive disturbances .

Refractory Epilepsy is associated with poor quality of life, social stigma and poor school performance.

Epileptic syndromes:

A syndrome is a group of symptoms and signs occurring at specific age, follow specific pattern of expression and inheritance. When taken together, they help to diagnose and prognosticate

Significance of the epileptic syndrome:

- Epileptic syndromes constitute 10% of all childhood epilepsies.
- Prognosis varies from benign to grave
- May indicate underlying brain damage.
- Are an important cause of intractable epilepsy of childhood.
- Treatment is distinct/specific and certain syndrome need to be referred to higher centre for therapy .

CLASSIFICATION OF EPILEPTIC SYNDROME ACCORDING TO PROGNOSIS:(9)

Excellent prognosis.

Benign neonatal seizures

Benign myoclonic epilepsy of infancy

Benign rolantic epilepsy

Benign Occipital epilepsy

Benign Frontal epilepsy

Good prognosis

Childhood absence epilepsy

GTCS on awakening

Some localization-related epilepsies

Poor prognosis

West syndrome.

Lennox Gastaut syndrome

Sturge weber syndrome

Tuberous sclerosis ,

Rasmussen syndrome,

Progressive myoclonus epilepsies.

Uncertain prognosis

Juvenile myoclonic epilepsy

EPILEPTIC ENCHELOPATHY OR OHTAHARA SYNDROME:

- Early onset within the first few months of life frequent
- Tonic Spasms and burst suppression pattern both in waking and sleeping state, partial seizures may also occur.
- Prognosis is poor with refractory seizures.
- Associated psychomotor retardation is common.

- Often evolution of West syndrome at the age 4-6 months.
- The syndrome is associated with high mortality and morbidity with half the patient die within weeks or months.

WEST SYNDROME:

- The most common type of epileptic encephalopathy .Occurs in 3-5 /100,000.
- Age of Onset: 3-7 months of life.
- Male sex more predominant.
- Developmental delay is associated with it
- And Tuberous sclerosis is more commonly occurring with it.
- Clinical manifestations : Infantile spasms, cry at the end of spasms occurs in cluster 20 to 100 spasms occur per day .usually occur at the end of sleep or arousal.
- EEG : Hypsarrhythmia the archetypal pattern. Treatment Both ACTH.0.02-100units/m^2 and predinislone have been used

Severe Myoclonic epilepsy in Infancy or Dravet syndrome

- This is the severe form epilepsy, autosomal dominant, seizures start as early as 5 months of age before one year of age group.
- Epidemiology: 6 % of the epilepsies and incidence of 1/30,000 live births.

- Clinical presentations : Tetrad of all seizures : (a) Early infantile febrile convulsions (b) Myoclonic seizures (c)Atypical seizures (d)Complex focal seizures(e) atypical absence can occur in the patient.
- Occuring time : On arousal and alert state
- MRI: normal
- EEG: Poly spike slow waves Prognosis: Intractable seizures. Neurological decline occur.
- Managment : Carbamezipine, phenytoin, lamotrigine should not be used.

LENNOX GASTAUT SYNDROME:

- Occurs in 2-6 years of age,
- No family history of childhood epilepsy,
- Multiple seizure types –GTCs, tonic seizures almost always myoclonic, atypical absence, or atonic.
- Often evolve from west syndrome.
- Status epilepticus common.
- EEG Bilateral slow spike waves, slow background.
- Mental retardation is common.

- Management: broad spectrum AEDS like sodium valporate 50mg/kg, benzodiazepines, newer AEDs like lamotrigine, and topiramate can be used.

LANDAU KLEFFNER SYNDROME :

- Onset 3years -9 years
- Acquired aphasia-fluctuating or persisting word deafness,poor response to verbal language.
- Seizures are partial or generalized.
- EEG Bilateral temporal spike waves.
- No typical MRI findings. Avoid carbamezipine.
- Treatment- prednisolone 1.5 mg/kg over 4-6 weeks. Sodium valporate.

RING CHROMOSOME 20(rc 20 syndrome):

- It is a rare chromosomal abnormality associated with refractory epilepsy. It is at least one of the two chromosomes shaped as ring. Ring chromosome was first described by Atkins and co-workers in 1972[(15)].
- It constitutes 2-3% of all cases of epilepsy. 60 cases reported in the literature.[(15)]

- Ring chromosome is associated with loss of telomeric material on both sides of the chromosomes. The deleted region of chromosome 20 contains important and their loss leads to development of epilepsy.[15] p13 and q13 represents KCNQ2,CHRNA4 [15]. Ring chromosome is associated with frontal atrophy and frontal cortical dysplasia.
- The cardinal clinical features of chromosome 20 are epilepsy which is intractable, mild to moderate cognitive impairment and behavior There is no significant dysmorphism
- Seizure onset is typically at around 3 to 5 years of age. Seizures are partial seizures or generalized seizures or nocturnal frontal lobe seizures,
- Genetic testing: By karyotyping analysis.
- EEG: High amplitude Rhythmic slow delta waves 2-3 HZ with spikes and wave discharges arising from both frontal areas.
- Imaging: MRI shows frontal atrophy.

Inverted duplicated chromosomes 15 [isocentric chromosomes] idic[15]

- The syndrome is the complex neurogenic condition characterized by early central hypotonia, developmental delay and intellectual disability epilepsy and autistic behavior.

- Incidence is 1/30000 with equal predilection for both the sex.
- The chromosome region 15q11-q13 is prone for genomic rearrangements due to repeated DNA elements[16]. idic (15) distinct behavior has been autistic. They are fascinated by some sounds, by water, by spinning or any glittering objects, they like to be left alone, outburst of shouting and aggressiveness is present. Stereotype behavior is commonly associated.
- Muscle Hypotonia, joint hyper extensibility with minor facial dysmorphism are the presenting features.
- Epilepsy age of onset 6 months to 9 years. Associated with absence like seizures or myoclonic absence can be seen.
- EEG: Frequent large amplitude, generalized paroxysms, lasting for 2-20s by slow sharp elements spike wave complex accompanied with absence.
- MRI: normal
- Genetic test: Karyotyping with FISH analysis will be useful to find out the abnormality.
- Drug of choice: Valproate with lamotrigine, Carbamezipine with lamotrigine if associated with tonic seizure

PATHOPHYSIOLOGY OF EPILEPSY

'EPILEPTOGENESIS' is an operational term referring to the time period between the brain insult and the appearance of the first seizures. It refers to the dynamic process that progressively alters neuronal excitability and establishes critical interconnections and structural changes before clinical signs appears.

Pathophysiology :

Electrical activity of a seizure is a net product of biochemical processes at the cellular level causing 1.Neuronal Hyperexicitability 2. Hypersynchrony.

Hyperexcitability- 'reduced threshold for neuronal firing'.

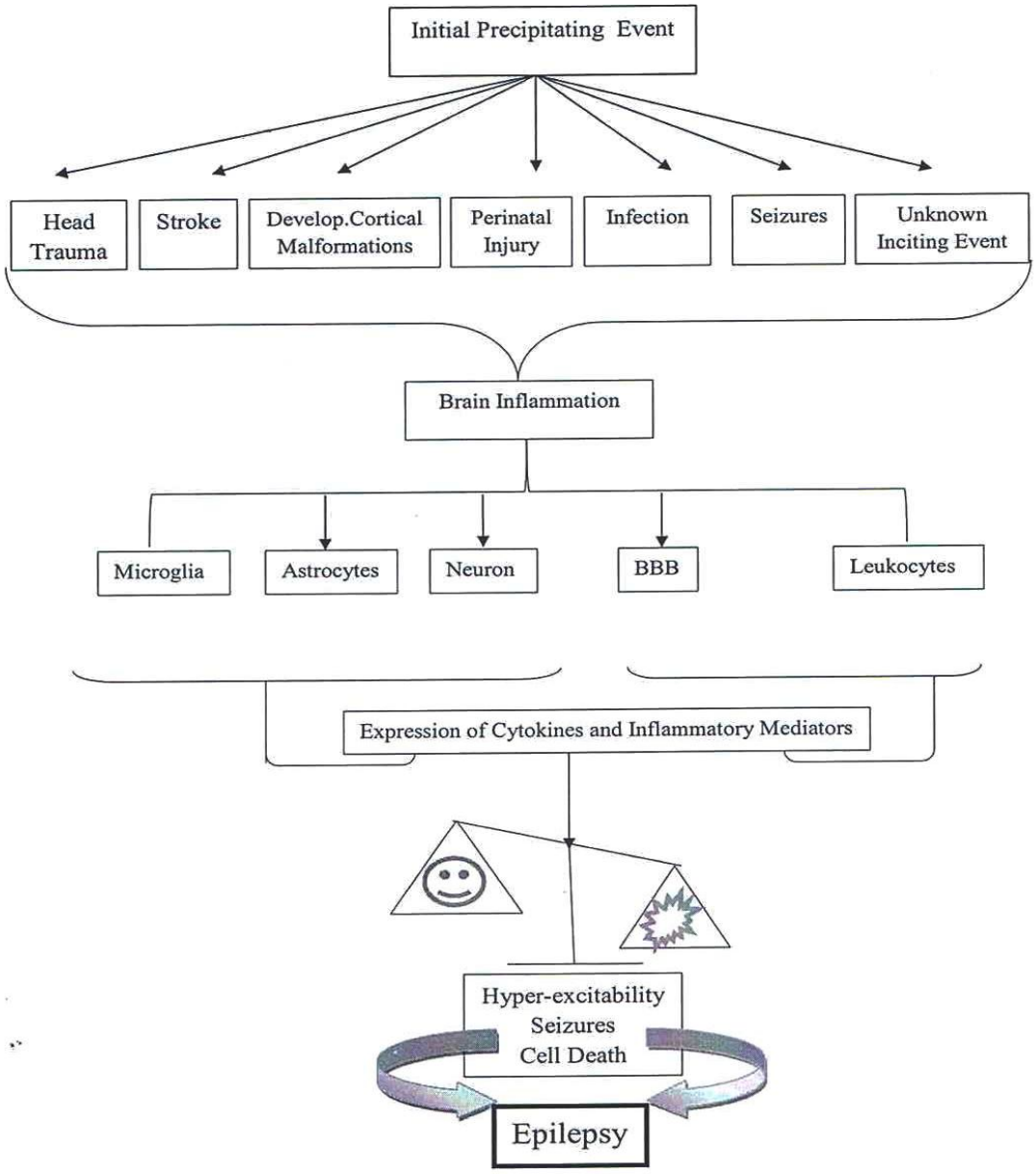
Hypersynchrony- 'neurons in a given area firing to gather'

Mechanism of hyperexicitability :

Proinflammatory condition increases neuronal hyperexicitability by

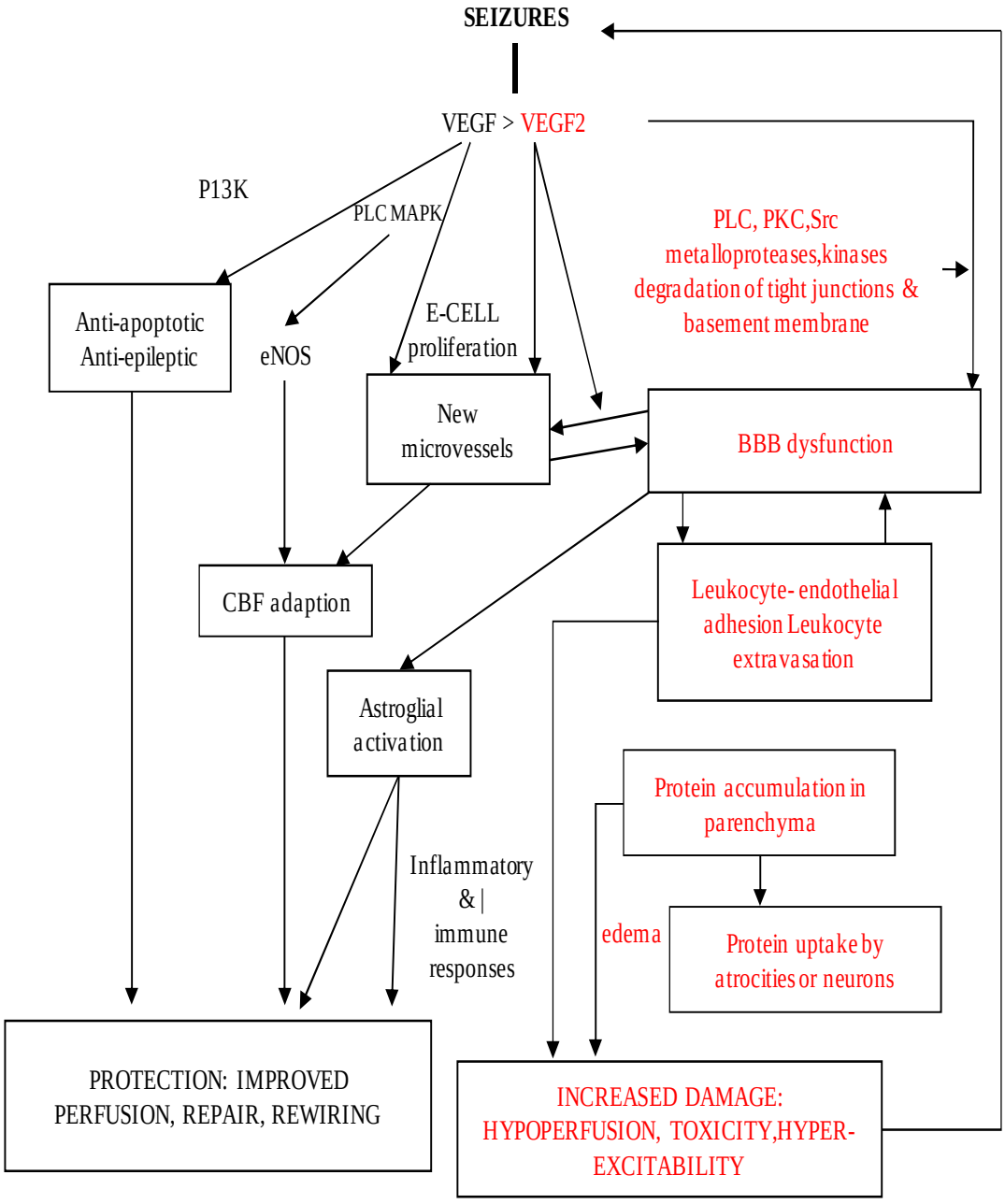
1. Increasing extracellular glutamate either by inhibiting its uptake or by promoting its release from atrocities.
2. Cytokines increases ca^{2+} permeability of NMDA and AMPA receptors-gated channels
3. Cytokines and prostaglandin directly alter voltage-gated and ligand–gated ion channels.
4. Cytokines promote endocytosis of $GABA_A$ receptors and inhibition of GABA-mediated Cl^- fluxes.

Figure - 1



Schematic representation of the cascade of inflammatory events that are triggered by brain injury eventually resulting in epilepsy[52].A large variety of injuries occurring at birth or during infancy intiates the cascade of chronic and self sustained inflammatory events in the brain contributes to the late onset epilepsy.

Figure - 2



The deleterious pathways in red are VEGF-2 are deleterious by blocking anti apoptotic effects (PLC, PKC, Src) and participate in the vascular permeability by degradation of the basement and tight junctions. Blood brain barrier permeability promotes epileptogenesis.*

Epileptogenesis in the Developing Brain

Seizure is common in the first decade particularly in the first year of life. Multiple physiological factors play a role in increased susceptibility of the developing brain to seizures,

Factor	Consequence
Increased input resistance and time constant in immature brain	Small inputs results in large voltage changes
Voltage-gated ion channels: earlier maturation of sodium and calcium channels, delayed development of K channels	Longer action potential, shorter refractory periods, increased neuron firing
Excitatory synapses appear before inhibitory synapses	Predominance of excitation over inhibition.
Over expression of excitatory synapses during critical period	Heightened seizure susceptibility
Developmental changes in glutamate receptor subunits NR2B/NR2A favours prolonged depolarization,NR2D over expression reduces mg^{2+} block	Favours hyperexicitability
$GABA_A$ binding pattern in substantia nigra	Pro convulsant effect
Developmental changes in $GABA_A$ receptor subunit	Decreases inhibitory effect
Developmental sensitivity to glutamate toxicity	Decreased excitotoxicity
Immature homeostatic mechanismNa^{2+} K^+-ATPase, glial K^+regulation, K^+ Cl- cotransporter	Prolonged exposure to K channels causing neuronal network

NEONATAL SEIZURES:

Neonatal seizures are most important presentations and it signifies neurological dysfunction. Immature brain is more prone for seizures. There are five types of seizures: subtle seizures, clonic, tonic seizures, myoclonic and spasms. Of which generalized myoclonic seizures, focal tonic, focal clonic and spasms are prone for epileptic seizures.

Etiology:

1. HIE(Hypoxic ischemic encephalopathy)
2. Vascular cause like subarachnoid hemorrhage, inter ventricular hemorrhage
3. TORCH-intracranial infection
4. Brain malformation like Neuronal migrational disorder,Aicardi syndrome etc
5. Metabolic disorder, IEM

Neonatal seizures-focal seizures generalized myoclonic, infantile spasms must be evaluated in a proper ways. MRI is recommended in neonates with microcephaly, unknown cause after ruling out hypoglycemia, hypocalcemia etc.

STATUS EPILEPTICUS

Operational definition - “one continuous generalized, convulsive seizure, lasting for more than 5 minutes or two or more seizures during which the patients does not return to baseline consciousness.”

- Acute repetitive seizures [ARS] or Cluster seizures, Serial seizures, flurry seizures] is “a multiple generalized tonic clonic, or tonic-clonic seizures or multiple partial seizures with or without generalization occurring over brief period [24 hours]”
- REFACTORY STATUS EPILEPTICUS; “Status not responding to medications for 60 minutes or two or three drugs, one being benzodiazepine.”
- NCSE; “Non Convulsive status epilepticus are described as children appearing forget full and sleepy, sometimes associated with falls, poor motor control, abnormal balance”.

Incidence:

75%-80% of pediatric status occurs < 5 years of age and maximum being less than one year.

Status epilepticus is a common first presentation in infants and children.

10-25% of children with epilepsy and 5% with febrile seizures have at least one episode of SE. 12-15%of the newly diagnosed epilepsy present with SE.[21]

TYPES OF SE:

Partial status epilepticus

Generalized status epilepticus

Non convulsive status epilepticus

NON CONVULSIVE STATUS EPILEPTICUS

NCSE is described as forgetful and sleepy appearance.

NCSE with special epilepsy syndrome and encephalopathies:

Dravet syndrome, myoclonic astatic, malignant migrating partial epilepsy of infancy Lennox–Gestaut syndrome, Angelmans syndrome, Ring chromosomes20 rc syndrome[22]

Newer epilepsies with status epileptcus;[23]

FIRES - "Fever Induced Refractory Epileptic encephalopathy in School aged children"

AERRPS – "Acute Encephalopathies with Refractory Repetetive Partial Seizures"

DESC - "Devastating Epileptic encephalopathy in School aged children."

NORSE - "New onset Refractory Status epilepticus"

PCDH – "X linked protocadhering -19 mutations" early childhood seizures and status

POLG1 - "Alpers .Hunter locher syn, infantile severe epileptic encephalopathy with hepatic involvement.

COMORBIDITIES IN REFRACTORY EPILEPSY:

Cognitive and Behavioral disturbance are the most common co-morbid conditions of the patients with RE which is usually associated with early onset seizures, severity of seizures, lower socioeconomic class, longer duration etc

Common behavioral symptoms being ADHD, hyperactivity, ASD-Autistic spectrum disorder, depression, learning difficulty, low memory, problem solving etc

AEDs associated with cognitive and behavioral symptoms are Phenobarbitone - being maximal effect, followed by sodium valproate, carbamezepine and second generation AEDs like topiramate, gabapentin, lamotrigine.

Attention deficit hyperactivity disorder (ADHD):

ADHD is a" severe inattention, hyperactivity and impulsivity". All three findings in 80% only inattention in 10-15% impulsivity in 5%. ADHD pre dated the seizures and 2.5 times more likely to have seizures. The bio mechanism shows increased frontal gray matter and decreased white matter [(24)]. Drug of choice is Methylphenidate. Appropriate AED must be prescribed along with methylphenidate. Dopamine abnormality is the primary cause for ADHD.[(24)]

MANAGEMENT OF REFRACTORY EPILEPSY :

ANTIEPILEPTOGENESIS' is to prevent or delay the epilepsy and also to reduce the severity and reversal of drug responsive epilepsy.

The proper diagnosis is the first step in the management, which gives the clue for selection of appropriate antiepileptic[25.]

Epilepsy seizure type	First AED	Adjunctive AED	Drugs to be avoided
Generalized tonic –clonic	Carbamezepine, lamotrigine, oxacarbazepine sodium valproate levetiracetam	Clobazam, topiramate	
Atonic	Sodium valporate	Lamotrigine	Carbamezepine, Gabapentin, Pregabalin
Myoclonic	Levetiracetam, sodium valporate lamotrigine	Topiramate zonisamide	Carbamezepine, Gabapentin, Pregabalin
Focal	Carbamezepine, lamotrigine, oxacarbazepine sodium valporate levetiracetam	Topiramate, Gabapentin, clobazam	
Epilepsy syndrome			
Epilepsy with generalized tonic clonic seizures.	Carbamezepine, lamotrigine, oxacarbazepine sodium valporate	Levetiractam Topiramate clobazam	

Infantile spasms without TSC	Steroids vigabatrin	Pyridoxine	
Infantile spasms without TSC	Vigabatrin or steroids (predinisolone, tetracosacide)		
Drave syndrome	Sodium valporate, topiramate	Clobazam, stiripentol	Phenytion, pregabalin, Gabapentin Carbamezepine, lamotrigine, Oxacarbazepine
Lennox Gastaut syndrome	Sodium valporate	Lamotrigine Rufinamide Topiramate	
Landau Kleffner syndrome	Steroids	Clobazam. levetiracetam, lamotrigine	

SURGICAL MANAGEMENT IN EPILEPSY:

Surgical management is the evolving trend of Epilepsy

Resective surgery: Only one single focus in non eloquent region. e.g.temporal lobectomy.

Palliative surgery to prevent spread of seizure discharges.

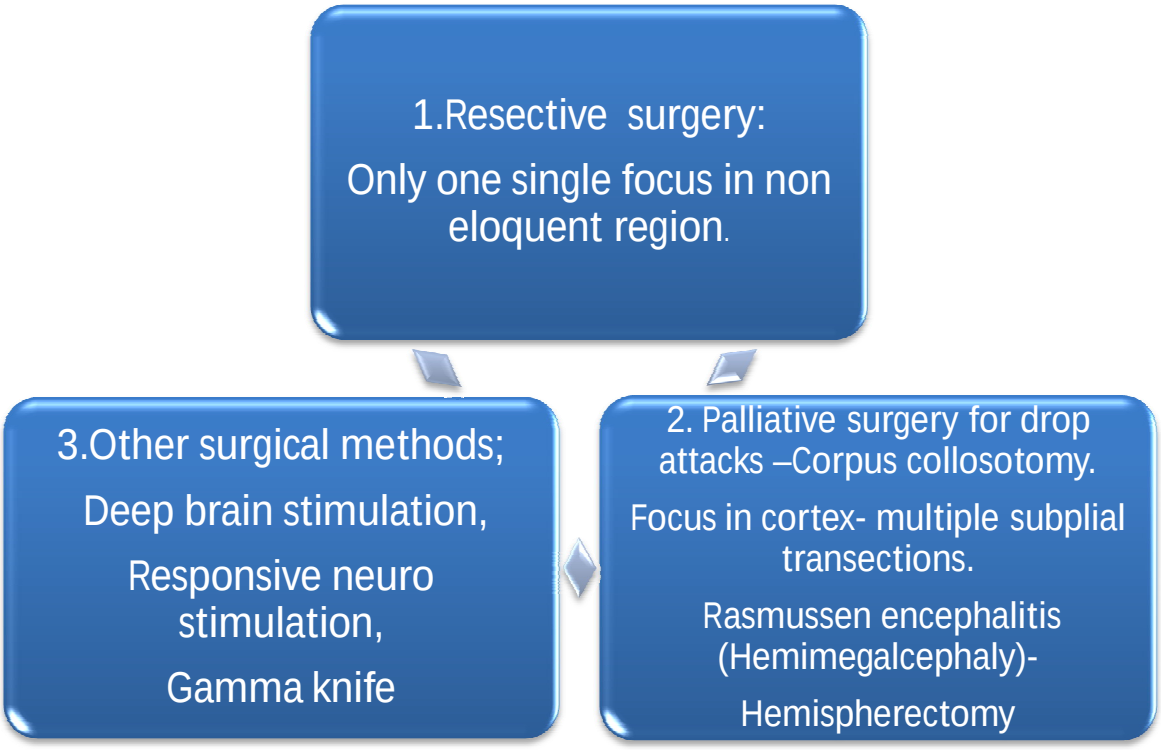
1. Drop attacks –Corpus collosotomy.
2. Focus in eloquent cortex multiple sub-pial transections
3. Rasmussen encephalitis, Hemimegalcephaly-Hemispherectomy

Other surgical methods:

1. Deep brain stimulation
2. Responsive neuro stimulation
3. Gamma knife

Limitations :

- Expensive, not universally available.
- Not all intractable epilepsies are amenable to surgery.
- Risk of post surgical neurologic deficit.



OUTCOME

First unprovoked seizure in childhood, recurrence rate is 40%, after second seizure, the risk increases to 80%. Normal child presenting with first GTCS and normal EEG has recurrence risk of 20-30% and a child with developmental delay recurrence rate is 80-90%.

Patients with Refractory Epilepsy should undergo evaluation to confirm diagnosis to prognosticate the outcome. Most patients can be identified early and proper management prevents the recurrence.

Children with RE has increased risk mortality and co-morbid condition like hyperactivity, ADHD, poor school performance, so needs aggressive management.

QUALITY OF LIFE IN EPILEPSY PATIENTS

Quality of life includes social, physical, psychological and academic function. Risk factors for poor QOL is the refractory epilepsy and associated risk factors like

1. Early onset seizures
2. More severe seizure
3. Increased frequency
4. Associated Co morbid conditions
5. Low socio economic class
6. Side effects of AED’s

Impact of refractory seizures on the Family and Society, including children:

First response of the family members to the diagnosis of a seizure disorder in children is sadness, anger, anxiety, fear etc, They are worried and bothered about the disease outcome, negative response in the school and about the long term use of the AED's.

Children feel away from the wards, for the reason of being teased by the peers. School abstinence due to admissions in the hospitals for seizure, affect their intellectual capability. One third of the children require special education also.

Children with refractory seizures should restrict extracurricular activities. They should avoid

1. Swimming unattended
2. Playing with sharp objects
3. Playing in open terrace, climbing up trees
4. Playing or cooking near the open fire
5. Avoid risky activities

Precautions against injury and advice to the parents

Precautions for the children: kitchen - avoid playing with sharp objects.

- Bathroom : avoid bubble bath, bathrooms closed from outside.

- Bedroom : lie on the mattress on the floor and use firm pillow to avoid suffocation.
- During ictal, postictal periods: parents should place the head in raised position on the cushions and ensure that the airway is not obstructed.

When to call for help:

1. Respiratory disturbance,
2. More than one focal seizures,
3. Seizures of more than 5 minutes,
4. If recovery phase exceeds 2 hours,
5. Burns or injuries.

Role of imparting knowledge about epilepsy and outcome of refractory seizures

Parents must be educated to overcome the frustration, anger, myths about refractory epilepsy, they should be taught to work through the problem, raising the self regulation and self esteem. Good seizure control is the key for preserving intellectual skills, so the parents should be educated not to miss the AEDS, and accept the long term therapy. This is going to improve the academic outcome in the school and plays an important role in self esteem and self confidence, increase the competitive capacity.

Impact of refractory seizures on sexual development

Hormonal changes in the early puberty and menstruation have a negative impact on the epilepsy, so parents must be educated about the importance of continuing the AEDS in the proper way. Parents botheration on the long term use of AEDS and the side effects like weight gain, irregular periods, multicystic ovaries, hirsutism must be counseled properly and should be informed that the side effects outweigh the complications of the refractory seizures .

Parents should be made aware of behavior disturbance and the dependency on the parents for better outcome. They must be given behavioral therapy as soon as possible and in a sincere way. Good control of seizures results in a good behavioral outcome.

Approximately 75% of epileptic patients are well controlled with currently available antiepileptic drugs leaving 25% uncontrolled.[26] Although 24% drug resistant epilepsy patients experience remissions for >1 year, the treating doctor should refer them for pre surgical workup because two randomized controlled studies revealed surgical therapy is more beneficial than continuous chronic drug treatment.

A delay in referral increases the burden of epilepsy for the overall population, and reduces life spans and quality of life for individual patients

AIM AND OBJECTIVES

AIM

To identify the risk factors of refractory childhood epilepsy.

OBJECTIVE

To identify the association of karyotyping analysis in refractoriness.

To determine the prognosis of seizures in refractory childhood epilepsy

REVIEW OF LITERATURE

Management of Refractory epilepsy puts forward a great challenge due to the difficulty in understanding the resistance to antiepileptic drugs. Refractory epilepsy with status required frequent hospitalization having shortened lifespan and psychological impairment was considered in Landmark study by Kwan and Bordie of 525 patients over 13 years in the age group of 9-93 years. The results of this showed 63% with good drug control and 33% had treatment resistant seizures[31].

"Semah et al did observational study of 2220 O.P patients. This study concluded idiopathic generalized seizures had good prognosis and symptomatic generalized seizures had refractoriness [32].

This study was followed up at University of Pennsylvania with a different approach of 246 patients with refractory epilepsy and compared syndrome frequencies within the samples showed 80% localization related epilepsy, 11% LGS and 7% generalized[48]."

"Berg et al studied 599 children with newly diagnosed epilepsy for 30 months determined localization related epilepsy - 1.7% with lowest risk and symptomatic generalized epilepsy 55% with highest risk[33]. MTLE and dual pathologies presented with poor outcome. Multiple seizures before treatment had AED resistance and poorer outcome[33]."

Results of Udani et al's study of 123 children of RE showed age of onset <2 years, male sex, perinatal insults, neurological abnormalities, seizure syndrome, structural abnormalities had poor outcome [34].Multiple seizures prior to treatment radiological evidence, poor response to 1st AED were also associated with refractoriness[35].

In the same study 58 patients were analyzed for epilepsy surgeries outcome. Extra temporal resection resulted in 55% seizure free and hemispheric surgery with 64% seizure free. Palliative corpus callosotomy just decreased the frequency and severity of generalized seizures to 44%. In the same study 76% improved seizure frequency, behavioral improvement and 64% became attendive[36].

A case control study to identify the predictors of refractory epilepsy in North Indian population was conducted between August 2006 to December 2008 for a period of 2 ½ years with 200 cases and 200 controls by M.Tripathi et al with a data of history of febrile seizures, status epilepticus, perinatal history, family history, IQ, behavioral assessment CT, MRI, VEEG and SPECT[37].

The results of the study showed:

The comparison study showed males outnumber females		
	Controls	Cases
Partial	83%	56.5%
General	7%	30.5%
Myoclonic	6.5%	12.5%
Multiple	3.5%	
Status epilepticus	7%	2.5%
Febrile seizures	10%	2.5%
Developmental delay	18%	1%
Perinatal insult	23%	1%
Abnormal brain imaging	79%	39%

The study shows high seizure frequency prior to the treatment, neurological deficits, history of perinatal insults, status epilepticus, poor response to first AED, radiological structural abnormality, was significant in univariate analysis. Subjected to multivariate analysis showed structural abnormality, history of DD and early onset seizures were the real predicting factors[37].

The study was done in The Epilepsy centre of the children's hospital Lahore by "Muhammad Akbar Malik et al," from 2005-2007, a case control study with 506 children aged 1 month to 16 years with

idiopathic or cryptogenic epilepsy where 442 children were followed up intractability in 74% and 26% as control groups[38].

Result showed male gender as risk factor in refractory seizures similar to "Akhondian et al"[39] and controversial to "Kwan and Brodie"[40.] The next factor being the onset of seizures at < 1 year of age which agreed with "Berg et el"[41]and the increased >10 frequency of seizure prior to treatment similar to "Kwong et al "[42] But not with "Sillanpaa et al"[43] neonatal seizures had a worst outcome as per " Berg et al"[44,45,46] Myoclonic seizures and status epilepticus also had an association with intractability , EEG abnormality being strongly associated as per others.

A study was conducted by "Robert D Daber et al" in the "Department of Pathology USA" in 2012, has identified ring chromosome 20 syndrome present with absence of any dysmorphism, with only history of refractory seizures involving frontal lobe and seizures occurring at any time of the day with cognitive impairment . Ring chromosome 20 is due to telomere - telomere fusion which can be identified with newer genetic methods. According to them the seizures responds to valproate and lamotrigine. But has high risk of lethal status epilepticus and cognitive impairment[47].

"Hauser et al, the study to show the average prevalence rate of epilepsy to be 5.2 per 1000 population and the prevalence rate per 1000

population was 2.5, 4.4 and 3.6 in Kashmir Bangalore and parsis in Mumbai[49].

Another study by Shridharan and Murthy estimated the prevalence rate of urban and rural was 5.3 and 5.5 in Chennai[3].

The age adjusted prevalence was 5.3 per 1000 population based on met analysis of the community based studies in India.

K. Radhakrishnann et al[6] study concluded that almost 40% occurs in children; 50% in age group of 15-64 years and 20% in elderly people. Overall prevalence of 4.7 % in general population out of which the prevalence in males was 4.9 and among females it was 4.4 %.

Thomas SV et al from Sree Chitra Tirunal Institute of medical sciences and technology dept of neurology Trivandrum, India showed the results about Treatment gap which was 21% where most of the patients were on low dose poly therapy than a high dose monotherapy in the patients with poor seizure control and 25% of the required patients were not started treatment by the time of referral.

"V.Udani et al"[50]'s study done between May 2004 and August 2004, of 100 patients were recruited of which 67 were boys 37 were girls, and about the mean age of onset 13.9months, perinatal encephalomalacia found in 50 patients, including neonatal hypoglycemic brain injury in 23 patients; HIE in 8 patients; PVL in 7 patients; infarcts in 9 patients .multiple etiology in 3 patients. And 28 patients with migration defects,

TS. Metabolic etc, risk factors being LSCS, Low birth weight, poor feeding late new born feeding, etc was also associated

'Datta et al's study in a tertiary centre in south India in 2005 on the prevalence of various behavioral problems in children and adolescents belonging to the age group of 0-18 years with epilepsy showed that 53.8% were psychologically affected. The study was done on the basis of a cut off score on the Childhood behavioral check list which differentiated between psychopathology cases or non cases.

'Malgi et al's study in 2005 at a Tertiary center in north India showed that 39.5% of epilepsy patients were affected psychologically. This was done on the basis of the score in childhood psychopathology measurement schedule labeled as maladjusted.

'Prassouli et al' in 2008 at Greece concluded his report with 49.5% labeled as having behavioral and emotional problems on the basis of score on childhood Behavioral checklist

'Turkey et al 2008's Community based study in united Kingdom showed 61.5% Increasing seizure severity associated with emotional problem and depression, impaired cognition associated with hyperactivity inattention, conduct disorder , abnormal peer relationship.

'Choudary et al'Tertiary centre in north India 2014 43% ADHD commonest in refractory epilepsy.

STUDY JUSTIFICATION

The assessment of the risk factors plays an important role in the diagnosis, which is the first step in the management of refractory seizures. The factors that determine the outcome of RE are varied age of onset, seizure type, ictal, post-ictal phenomena etc.

Early intervention with appropriate AED is the most important factor for better outcome in epileptics.

Early prediction of risk facts of RE helps the physician in educating the parents and to counsel the family members about the appropriate and optimal treatment for that individual child.

This genetic era is confluent with biomarkers; hence genetic studies play an important role in prognosticating the outcome in RE.

Nowadays genetic studies are being done for selecting appropriate therapy for better outcome, because genetics play an important role in the metabolism of AEDs and also in arriving at a diagnosis.

The patients affected by drug resistant epilepsy have an increased frequency of co-morbid conditions, psychological dysfunction, stigmatization, poor quality of life and high risk of mortality and finally, reduced life expectancy.

It is essential to prognosticate the outcome in RE, so that much attention can be given to those children.

Children with RE require more focus and more time can be spent by the treating physician, thereby the quality of life of affected children with RE can be improved and the co-morbidities and consequences of RE can be prevented.

METHODOLOGY

STUDY DESIGN	**:**	DESCRIPTIVE STUDY
SAMPLE SIZE	**:**	CONSECUTIVE CASES ENROLLED DURING THE STUDY PERIOD
PLACE OF STUDY	**:**	INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN, CHENNAI
PERIOD OF STUDY	**:**	AUGUST 2014 TO SEPTEMBER 2015

MATERIALS AND METHODS

SELECTION OF SUBJECTS

Children with idiopathic or symptomatic epilepsy who are on two or more AEDs and who were in follow up in Neurology OPD and inpatients in medical ward at ICH&HC, CHENNAI during the study period from August 2014 to September 2015 were included.

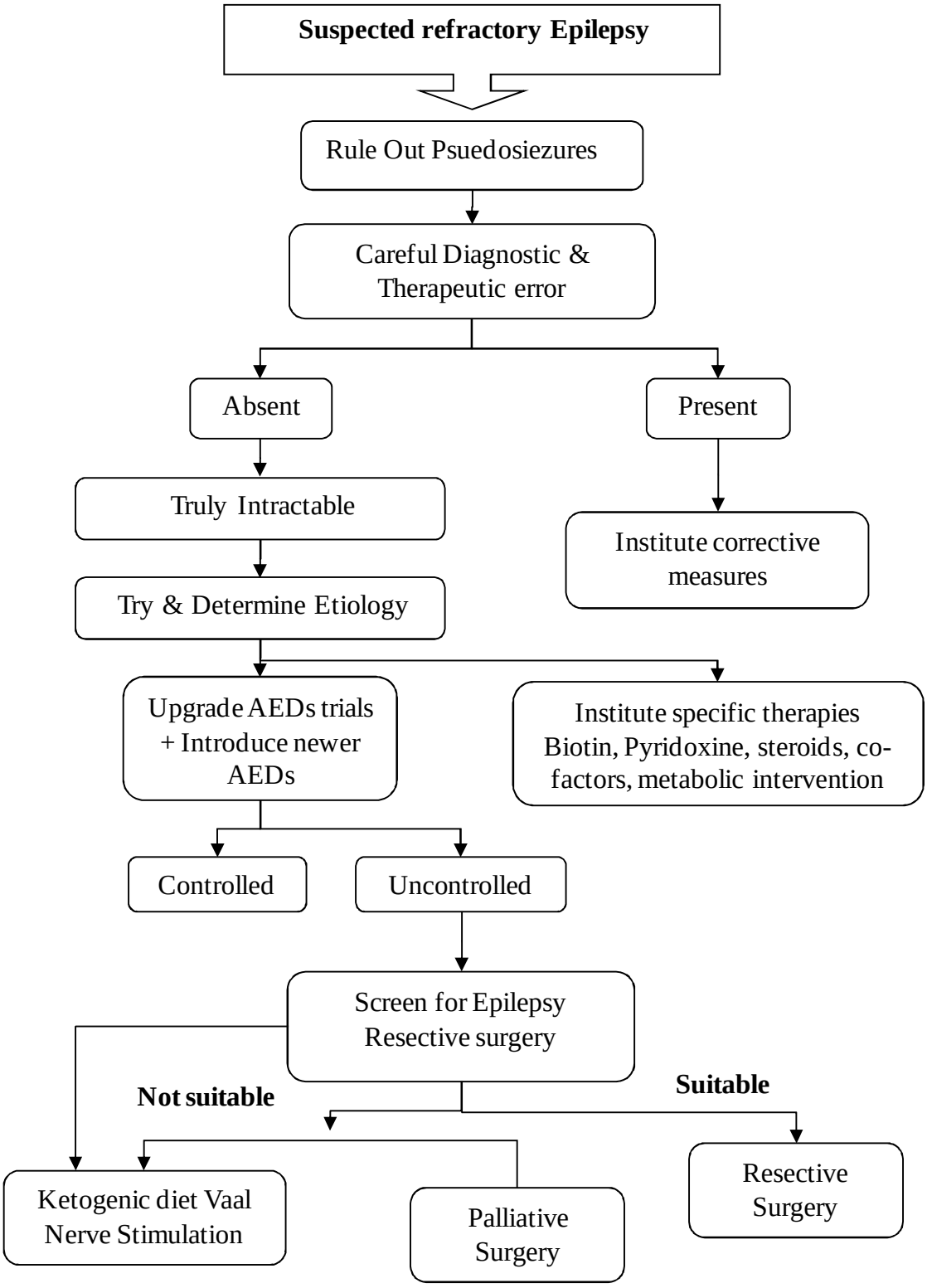
INCLUSION CRITERIA

Patients on adequate treatment with two AEDs either alone or in combination , with proper compliance and dosage.

EXCLUSION CRITERIA

Patients with poor compliance in the form of irregular medication or inadequate dosing were excluded.

APPROACH TO INTRACTABLE EPILEPSY



STUDY MANOEUVRE

This descriptive study was done in Department of Neurology, Institute of Child Health and Hospital for Children, Egmore Chennai. The study was done in the outpatient department of neurology and on in-patients, with refractory seizures, from age group of 6 months to 12 years after obtaining written consent and after counseling for karyotyping.

A pre-structured Questionnaire containing pre-defined variables was filled up, prior to their enrollment in the study.

Detailed history of seizure which includes the following:

Age of onset, type of seizure, number of seizures at baseline before starting treatment (per day/week/month/year, response to antiepileptic drug(s), longest seizure free interval, any history of status epilepticus (SE) before or as a part of presentation, hospital admissions and treatment, perinatal history, birth history, neonatal history, diet history, development history, associated symptoms (febrile convulsions, head trauma etc) and CNS infection were taken into account.

Family history of seizure disorder and history of poor scholastic performance, behavioral abnormality and focal motor deficits were also considered.

'A good history is as good as a diagnosis' detailed history and examination are very important for correct diagnosis. History taking

pertaining to the seizure episode including auras, autonomic symptoms, precipitating and triggering factors, motor phenomenon including generalization, focal seizures, tonic posturing, clonic jerks, Jacksonian march, versive head turning, tonic-clonic movements, myoclonic jerks, infantile spasms, drop attacks, post ictal phenomenon, time of occurrence of seizure were collected.

SEMIOLOGY OF SEIZURES - "study of signs"

Cleaveland epilepsy classification is a "Semiology classification method -which refers to study of symptoms and signs and behavior during seizure". This classification uses five dimensional assessment which gives a clue about the symptomatic zone of seizure appearance.

SEIZURE SEMIOLOGY

Classification	Symptoms	Localization
1.A.Somatosensory	Warmth Right hand'	Contralateral somatosensory area
	shoulders warmth,	[primary], SSMA,
	hands tingle,	Secondary sensory area sylvian fissure
1.B.Visual Aura	Flash spots on the right.	Contralateral primary visual cortex
	see birds on right	Contralateral association cortex.
1.C .Auditory Aura	Heer buzzing	Heschls gyrus
1.D.Olfactory Aura	Smell of burning rubber	Amygdala

1.E Gustatory	Taste bitter or awful	Insula or secondary sensory area
1.F. Autonomic Aura	Goose bumps ,heart races	Basal frontal region ‘insula
1.G.Abdominal Aura	Funny feeling in stomach	Insula . Sylvian fissure
2. Autonomic seizures	Goose bumps tachycardia ,palpitations .	Autonomic seizures
3.Dialeptic seizures [Absence seizures]	Vacant stare	Diffuse cortex ,vs. hippocampi
4 A.Simple motor		
A1.Myoclonic Seizure	Jerky	Primary motor cortex
A2 Clonic Seizure,	rhythmic tremor	Primary motor cortex
A3 Tonic seizure,	just twist upwards	contra- primary motor cortex
A4 Epileptic spasms	lurched forward	SSMARAS
A5 Tonic clonic seizures	grand mal	variable generalized
A6 Versive seizures	head eyes turning upwards	contra -primaryhemisphere between face and head
4B. Complex motor:		
B1 Hyper motor seizures	Rolling her shoulders up & down,	Frontal
B2 Autonomic seizures	Picking, smacking his lips	Temporal lobe epilepsy,
B3 Gelastic seizures	Laughs in weird way	Hypothalamic hamartoma
5.Special seizures		
5A Atonic seizure	Just goes limp does not get hurt	RAS Generalized,
5B Astatic seizure,	jerked back fell on face gets hurt	Variable
5C Hypomotor seizures	Baby stops moving suddenly	Variable
5D Akinetic seizures	Hand just stop working with left facial twitch	Contra hemisphere primary sup negative motor areas
5E Negative myoclonic	Hands up suddenly goes limp	poor localization
5F Aphasic seizures	suddenly stops talking and confused	Dominant hemisphere Cortical language area

Semiology gives information about epiletogenic zone. The new classification CEC consists of 4 spheres

1. **Cognitive sphere**- contains auras of sensory symptoms [visual déjà vu] along with EEG gives maximum information of the seizure type.
2. **Autonomic Sphere-** with autonomic symptoms.
3. **Consciousness Sphere-** Dialeptic seizures [Absence seizures]
4. **Motor Sphere**-motor signs predominate; classified as simple and complex type ; Special seizure is also in the classification.

SEIZURE SCORING SYSTEM

Engels seizure burden score give clue about the seizure frequency and disability. The score is a longitudinal scale from 0-12. Score less than 5 is associated with no disability and usually without the loss of consciousness and loss of muscle tone.score of 6-12 is associated with disability and intractability.

Seizure frequency	Score
Seizure free, off the AED	0
Seizure free, need for AED unknown	1
Seizure free, requires AED to remain so	2
Non disabling simple partial seizures	3
Non disabling nocturnal seizures only	4
1-3per year	5
4-11 per year	6
1-3 per month	7
1-6 per week	8
1-3 per day	9
4-10 per day	10
>10 per day but not status epilepticus	11
Status epilepticus without barbiturate coma	12

The parents or care givers are advised to video record the seizure episodes which helps in better classification.

NEUROLOGICAL EXAMINATION

Detailed neurological examination is done for all patients with Refractory Epilepsy. Examination includes inspection for neurocutaneous markers, head circumference measurement, assessment of higher

functions, examination of cranial nerves, eyes, tone, reflexes, examination of cerebellar system etc.

DEVELOPMENTAL DELAY

Definition

'Developmental Delay is implied if the child does not reach developmental milestones appropriate for that age in each / all domains. Developmental history plays an important role in assessment.

Age	Normal	Delay(>)
Social smile	1-2 months	3 months
Head holding	3-4 months	5months
Sit without support	5-8 months	12 months
Stands without support	8-10 months	18 months
Walks well	10-12 months	20 months
2-3 word sentence	21-24 months	36 months
Tells self name	30-36 months	48 months
Toilet control	42-48 months	60 months

Developmental Delay (DD) is global or selective. Selective DD involves delay in single specific domain (social/ motor/ language) is affected. Global developmental delay implies a delay that is more than 2 standard deviation below the mean for chronological age in 2 or more than two developmental domains, in children < 5years of age.

All high risk newborn admitted in the newborn unit were assessed and followed up in Child development Clinic. Newborns Denver score (0-6 years) is used to assess the development. Detailed history of antenatal period and perinatal period was included. The corrected gestational age was calculated for preterms and assessed accordingly. The rate of development, family pattern of development were also taken into consideration.

CSF ANALYSIS

Lumbar puncture can be withheld/ delayed in a child with subtle afebrile seizures. Patients with prolonged post ictal period, altered sensorium must undergo a lumbar puncture.CSF fluid was sent for biochemical study, cell count and culture sensitivity. In children with history of perinatal insult, with neonatal seizures, CSF glycine was done in suspected cases. In cases of suspected of CNS sections, viral studies including herpes, CMV, JE were also done.

ELECTRO ENCEPHALOGRAM

EEG is recommended in seizure cases for diagnosis. It is an important diagnostic tool in temporal lobe epilepsy. It gives the clue for the origin of seizures and the epileptic zone .To emphasize EEG is not a good substitute for good history but adds on to the value of diagnosis. Ictal EEG and interictal EEG were usually done. Interictal may only show

50-60% abnormality in the new onset seizures. This when repeated can identify up to 80% abnormality. EEG when taken within 24 hoursof the seizure episode shows abnormality.

Common types of waves:

1. Sharp waves 2. Spike waves 3. Slow waves 4. polyspikes
5. Phase reversal.

Common epileptiform abnormalities :

FOCAL SLOWING: slowing of ongoing activity in focal region in the hemispheric area is usually of structural abnormality, for example - gliosis, edema ,infarction etc. This type can be induced by hyper ventilation.

HYPSARRHYTHMIA: Back ground becomes disorganized, interspersed with high amplitude, chaotic and asynchronous slow waves with multifocal discharges occur in West syndrome, TSC etc.

GENERALIZED EPILEPTIFORM ACTIVITY: Discharges are generalized with variable frequency 1.5-3 Hz, slow spike waves complexes are typical of–LGS, 3 Hz spike and dome pattern occurs in absence seizures etc.

EEG recording in younger children demonstrates diffuse discharges. The discharge is focal or unilateral in older children.

Stereo EEG: This is safe but invasive. This is helpful in monitoring patients with refractory epilepsy, which aids in seizure localization even cases.

EEG is useful in diagnosis of epilepsy [axis1], gives clue for type of seizures [axis 2], Electroclinical syndrome [axis3],and also provides clues for etiology [axis4]. In all the patients with suspected refractory Epilepsy, EEG has been routinely done to prognosticate the outcome of the condition child and helps in the management, for selecting the appropriate AED.

CEREBRAL IMAGING

The imaging is done in suspected localization related epilepsy, in epilepsy syndrome. When the classification of epilepsy is in doubt. It is not routinely done in new onset seizure. In such cases MRI is preferred over CT scan for lack of radiation and superior resolution. Most of our patients with cognitive impairment and abnormal neurological examination have undergone elective and MRS. MRI epilepsy protocol helps in finding out the lesional epilepsy.

Magnetic Resonance spectrometry is a recent improvement. It measures the metabolites in the brain and analysis of the same and thus helps in the diagnosis of metabolic dysfunction. It gives clue regarding etiology. e.g lactate peak in mitochondrial disease, absence of creatine

peak in creatine synthesis disorder, N acetyl aspartate peak in Canavan's disease.

Diffusion Tensor Imaging (DTI) and Diffusion Weighted Imaging(DWI) are the recent imaging modalities in seizure. It demonstrates variation in cerebral whitematter integrity in active seizures with that of the recurrent seizure.

Functional MRI: Blood Oxygen level independent contrast imaging (BOLD) The BOLD response with EEG-fMRI is useful in finding the epileptogenic region.

High Field MRI scanners: 7 Tesla MRI is the most standard method for increased spatial resolution. PET and SPECT scans, the use of SISCOM (Subtraction ictal SPECT co registered to MRI) is of great value. These newer imaging will be considered in future.

METABOLIC WORK UP

Inborn errors of metabolism (IEM) are also associated with refractory epilepsy, it is mostly considered in patients with neonatal seizures. Metabolic disorders associated with epilepsy are mitochondrial disease, peroxisomal, lysosomal disorders, Menke's disease, carnitine deficiency, GLUT1 deficiency, multiple carboxylase deficiency, biotidinase deficiency, etc. Tandem mass spectrometry, urine for metabolic screening, urine for amino acids, serum levels of amino acids etc, and even genetic testing are done wherever necessary.

Autoantibodies in epilepsy: Cytotoxic T cells and antibody mediated activation play a role in neurodegeneration. Anti VGKC, anti-NMDA and anti GAD are also associated with refractory epilepsy. Studies are being done to know the association. TORCH panel is also done in the patients with perinatal insult and history of neonatal seizures.

HEARING ASSESSMENT

Prevalence of visual and auditory impairment is 25-50% in developmental delay; hence all children with refractory epilepsy are referred to ENT department for hearing assessment and speech therapy. Hearing assessment in new born is done by BERA, in older children by Behavioral observation audiometry and pure tone audiometry.

VISION ASSESSMENT

All children with Refractory Epilepsy were analyzed for visual impairments. Common errors associated were refractory errors, visual impairment, strabismus and retinal abnormality in preterm etc. Children were referred to RIO (Regional Ophthalmology Institute) Egmore, Chennai for evaluation.

BEHAVIORAL ASSESSMENT

Children with seizures are more prone for ADHD either because of the disease or due to drugs. Around 40% were associated with behavioral disorder. Children were referred to the Child Guidance Clinic in our

hospital, and the children were assessed by Vandenberg parent rating score , for behavioural abnormalities.

GENETIC TESTING

Genetic testing in RE is associated with more than 20 genes. Genetic testing may be used as a diagnostic testing and as well as predictive test and carrier testing in asymptomatic individuals with gene mutation (eg) KCNQ2,KCNQ3,SCN2A STK9 etc, Epilepsy can be associated with chromosomal defects like Down's syndrome, Angelman syndrome, Rett syndrome, ring chromosome 20, ring chromosome 14, Inverted duplication 15 syndrome etc. Epilepsy due to channelopathies, epilepsy associated with inborn errors of metabolism, and with cortical malformation is also associated with refractoriness.

KARYOTYPING

The subjects from our Institute both outpatient and inpatient are referred to The Tamil Nadu Dr MGR university Genetics department, Guindy Chennai. During the study period, 35 patients with idiopathic cause of refractory seizures with normal and abnormal phenotype were randomly selected and subjected to karyotyping which is done by collecting the venous blood in aseptic manner after informed consent.

METHODOLOGY OF KARYOTYPING

Steps

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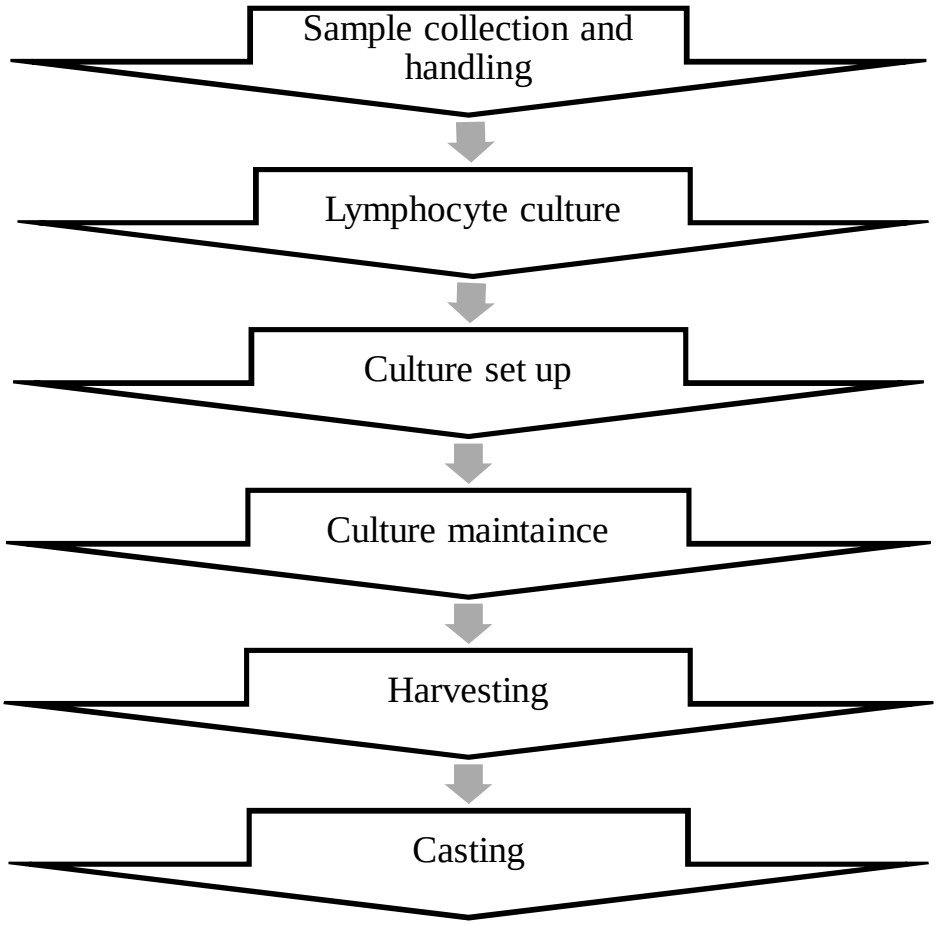
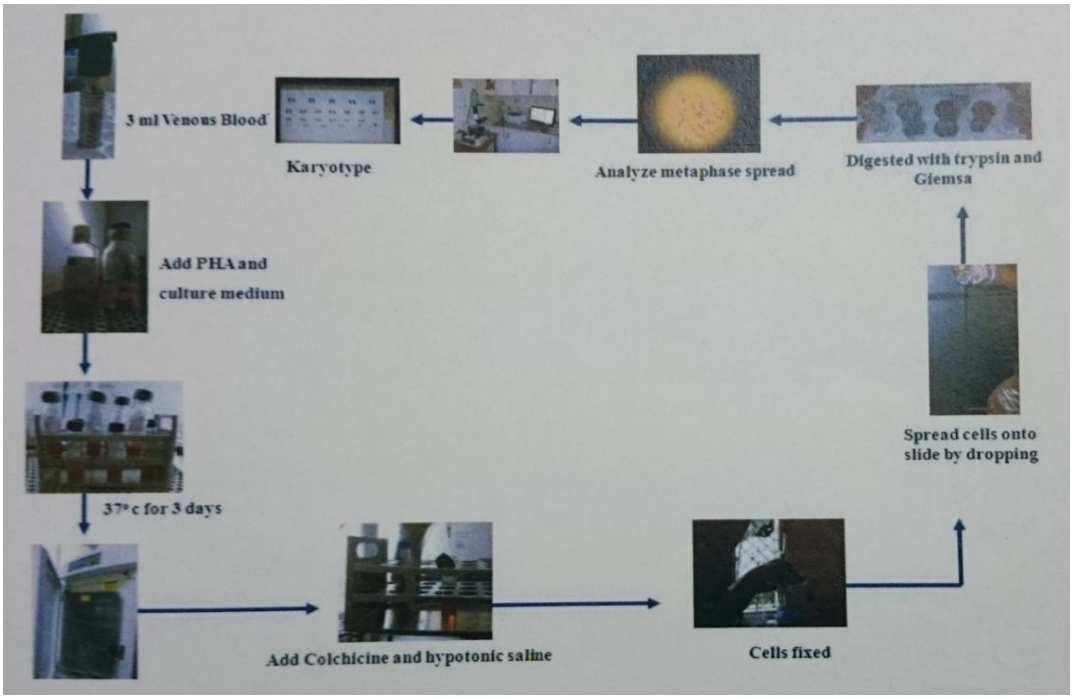


G-Banding (Giemsa Banding)is a technique used to obtain the karyotype by staining condensed chromosomes, with this method aged slides (7 days Old) are treated with the enzyme trypsin, washed with Sorensens buffer and stained with Giemsa stain, rinsed with distilled water and allowed to air dry. The air dried slides are mounted using DPX and analyzed under microscope.

In this produces a series of light and dark bands that allows identification of the chromosomes. A_T rich dark bands are late replicating bands, C-G bands contain relatively active genes.



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Chromosomal Abnormalities are of numerical and structural:

- Numerical includes loss or gain of single chromosomes, monosomy or trisomy or gain of complete set of haploid chromosomes, triploidy.
- Structural abnormality includes translocation, deletions, rings, inversion, isochromosomes, mosacism, chromosomal imbalance involving one or more of the autosomes. It gives very serious adverse effects.

A chromosomal aberration in which epilepsy can be the only expression of the disorder can be diagnosed by karyotyping. Constitutional ring chromosomes result from rare intra-chromosomal fusions and it occurs in about 1 in 30,000 to 60,000 births. Ring chromosomes arise from unstable telomeres or subtelomeric breaks on chromosomes that resolve and stabilize by circularizing.

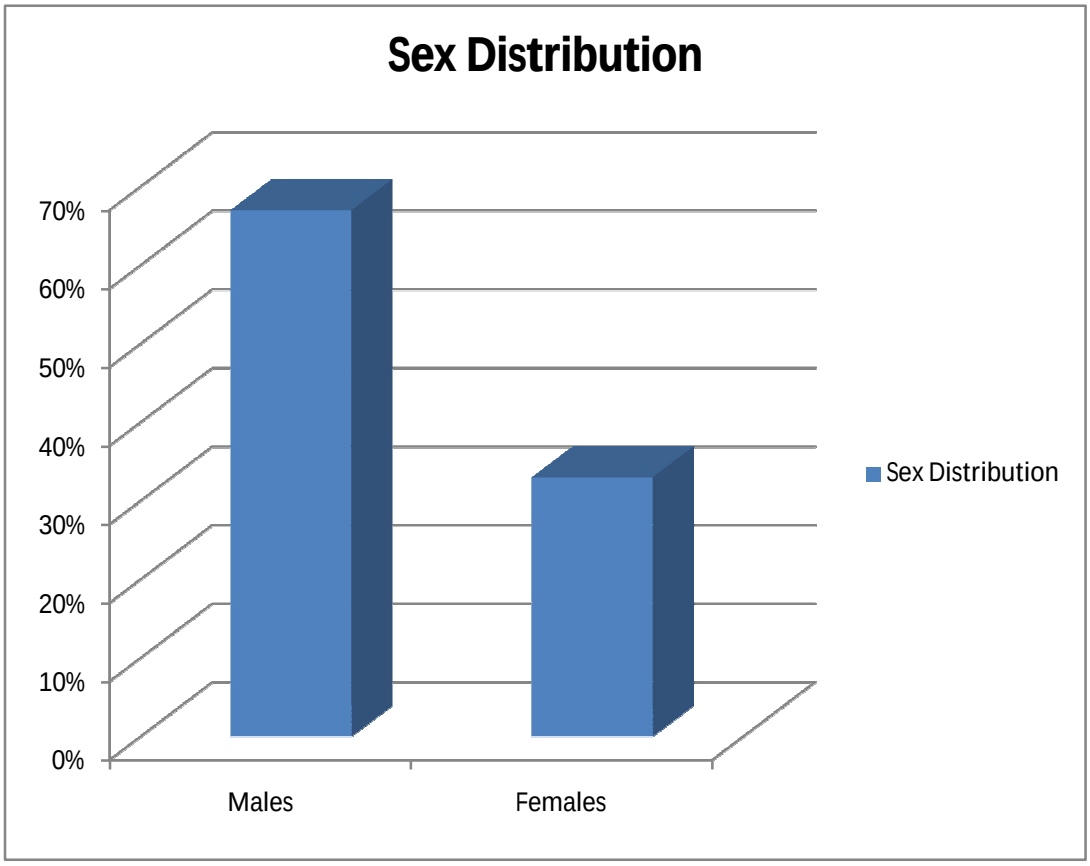
Ring chromosome 20 is a rare chromosomal abnormality characterized mainly by refractory epileptic seizures, cognitive and behavioral problems and absence of definite syndromic features[4].

STATISTICAL ANALYSIS

The clinical data and lab data of this study were entered in MS OFFICE EXCEL spread sheet and data were analyzed by using statistical package for social science SPSS- version 20.0

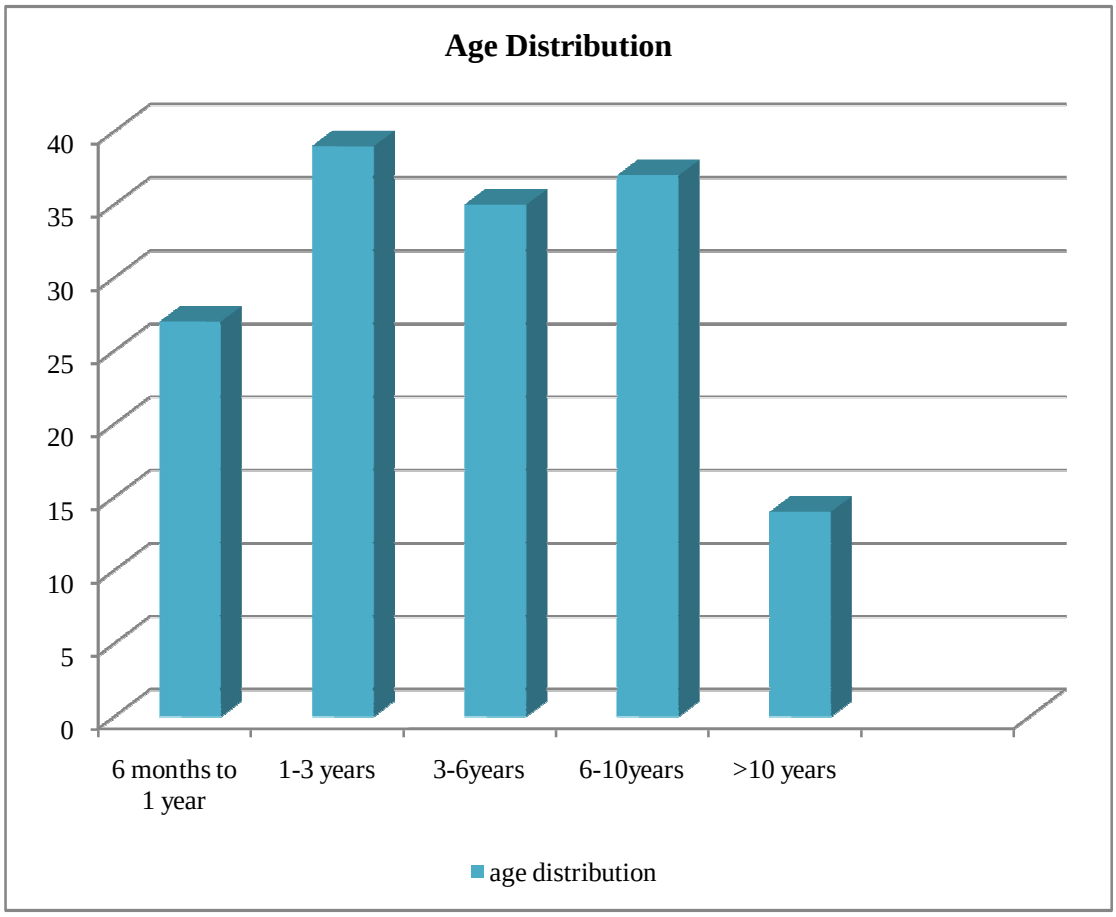
RESULTS

SEX DISTRIBUTION



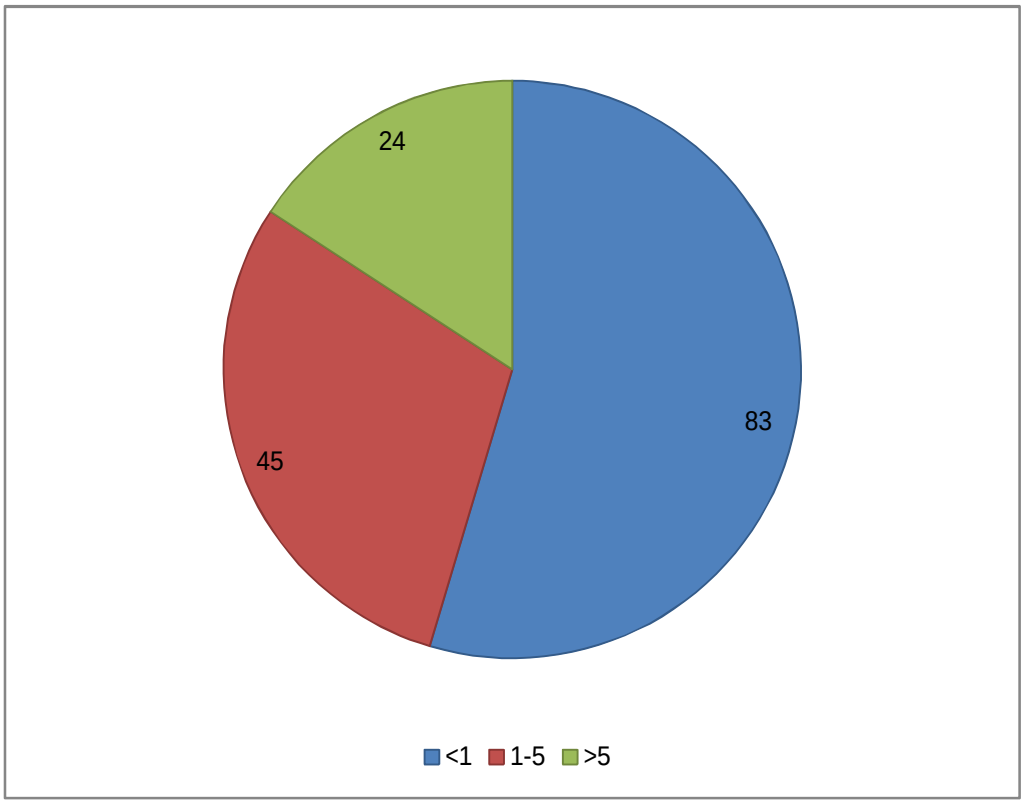
Males – 102 (67%) Females – 50(33%) Males predominating with 2:1 ratio

AGE DISTRIBUTION



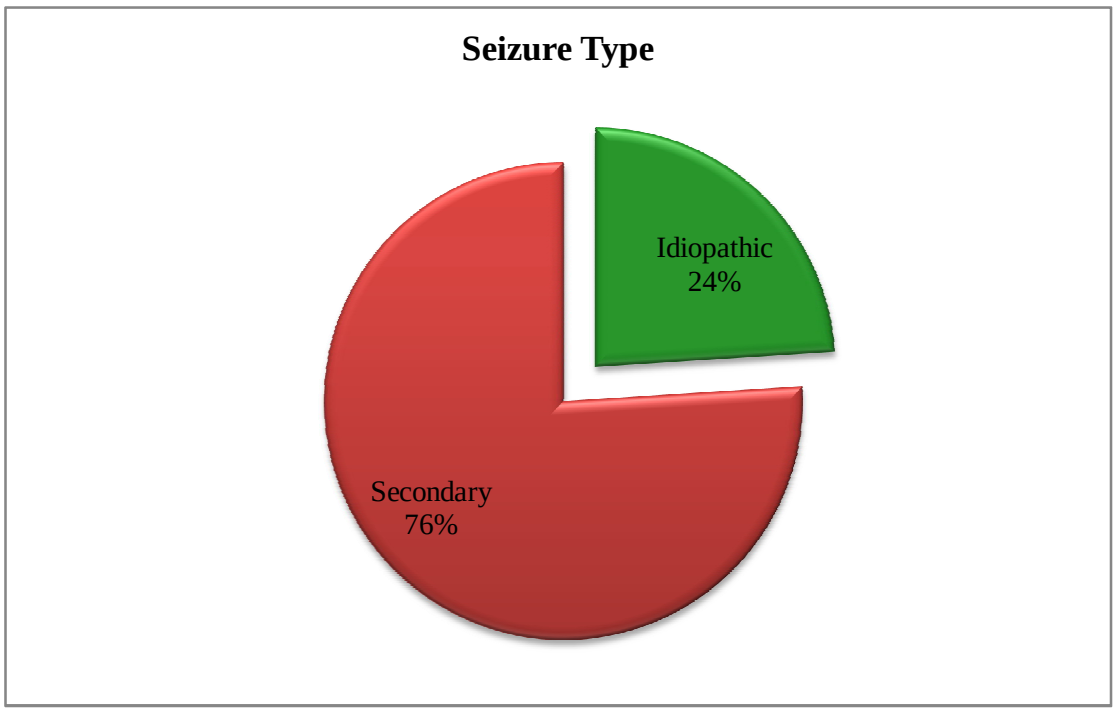
Children less than 3 years were the major proportion with refractory epilepsy in our study. 6months-1year27(17.8%), 1-3 years 39(25.7), 3-6 years37(24%), 6-10years 37(24.3%), >10years 14(9.2%).

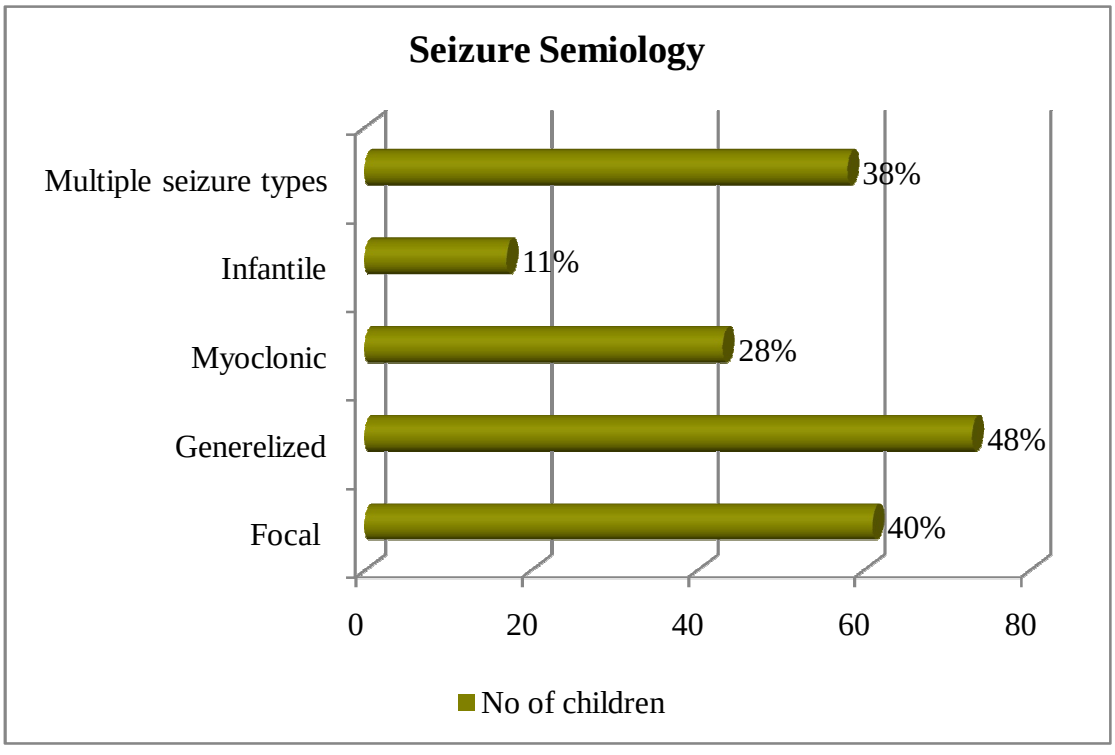
AGE OF ONSET



Age less than 1year - 83(54.6%), 1-5 years-45(29.6%), >5years-24(15.8%) age less than 1 year of onset has the significance.

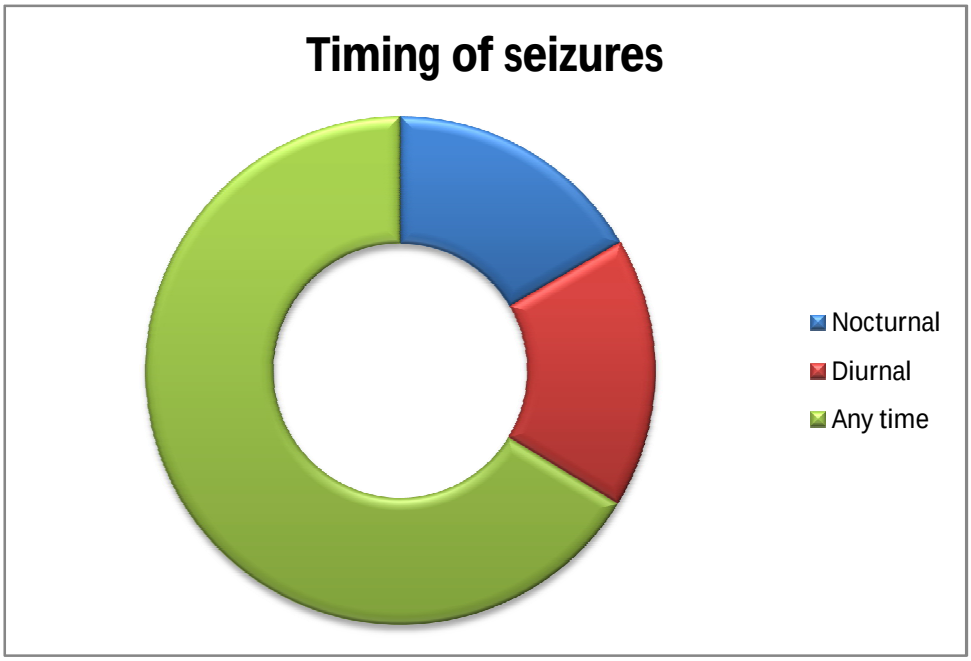
SEIZURE SEMIOLOGY





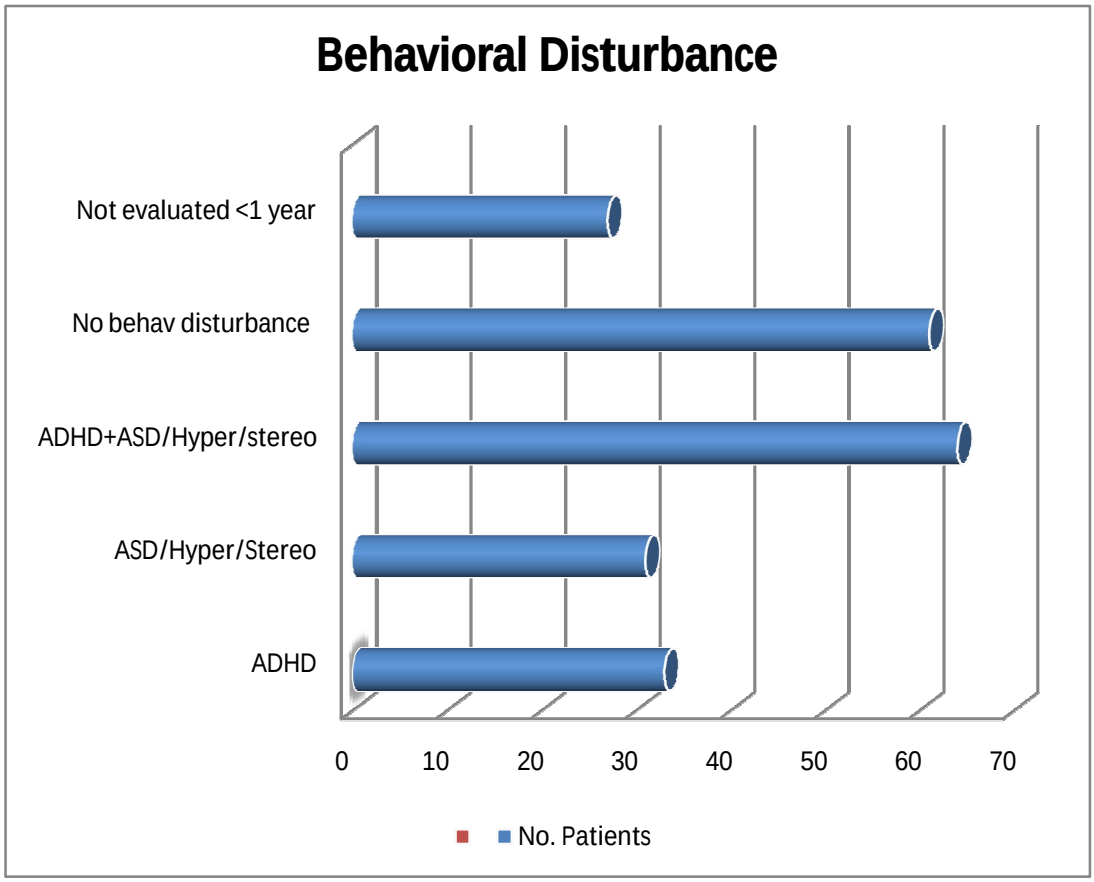
On analyzing the detailed history of auras, autonomic symptoms, ictal and postictal events, timing of seizure activity and precipitating factors, generalized seizure type (73) was the most frequent type, followed by focal seizures (68). Multiple seizure was the third most common type followed by myoclonic seizures.

Timing of Seizures



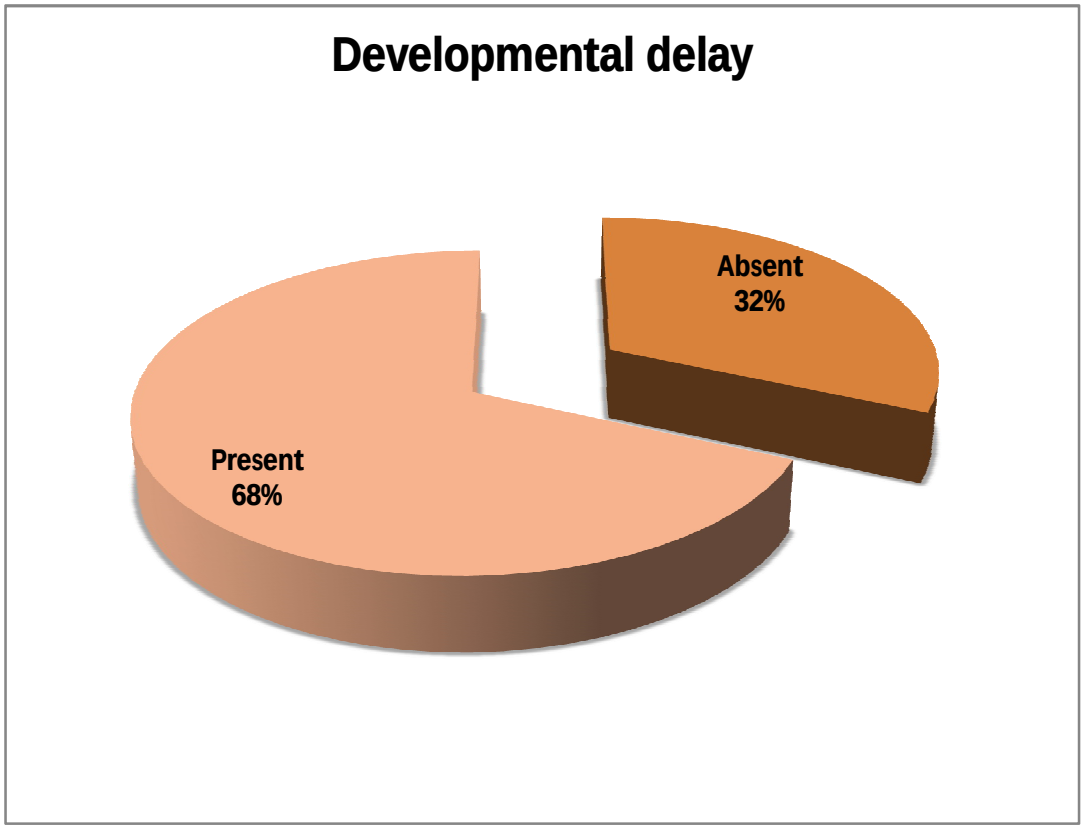
100(69.79%) patients had seizures irrespective of the time. Diurnal occurrence in 26(17.11%) patients and 25(16.45) were nocturnal.

BEHAVIORAL DISTURBANCE



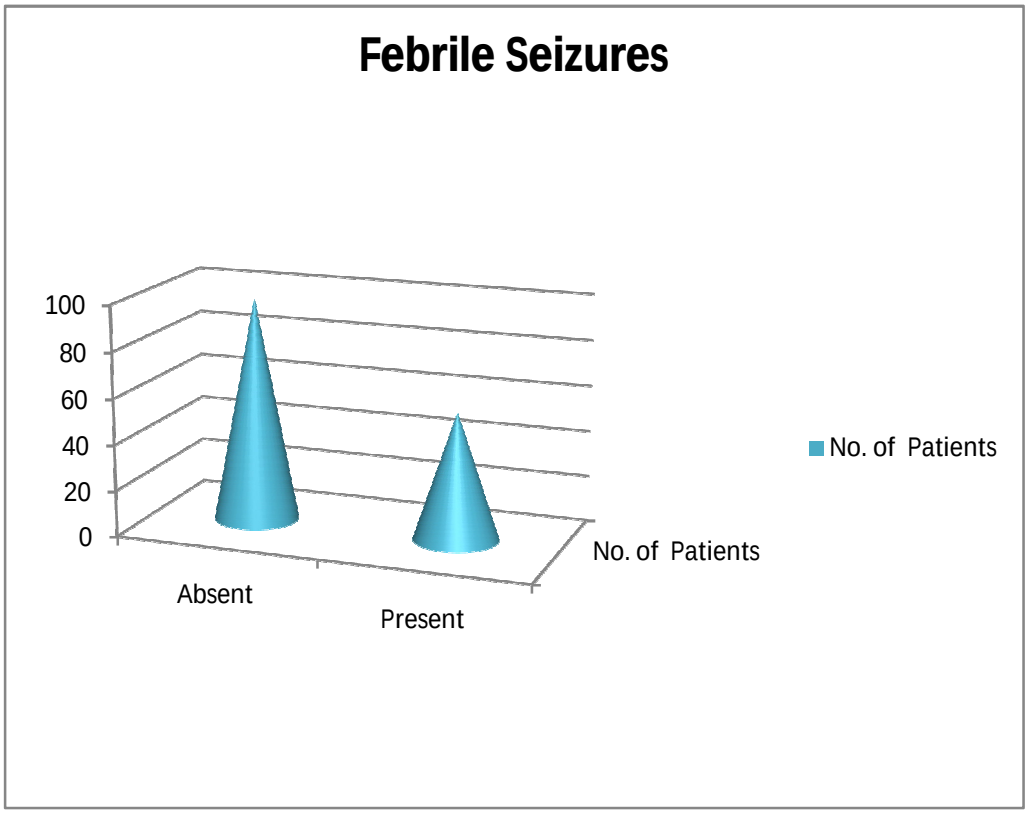
Out of the total 152 children with RE 64 showed significant behavioral disturbance. Out of 64 patients 33 had ADHD, 31 were found to have Hyperactivity, ASD and stereotypic behavior.

DEVELOPMENTAL DELAY



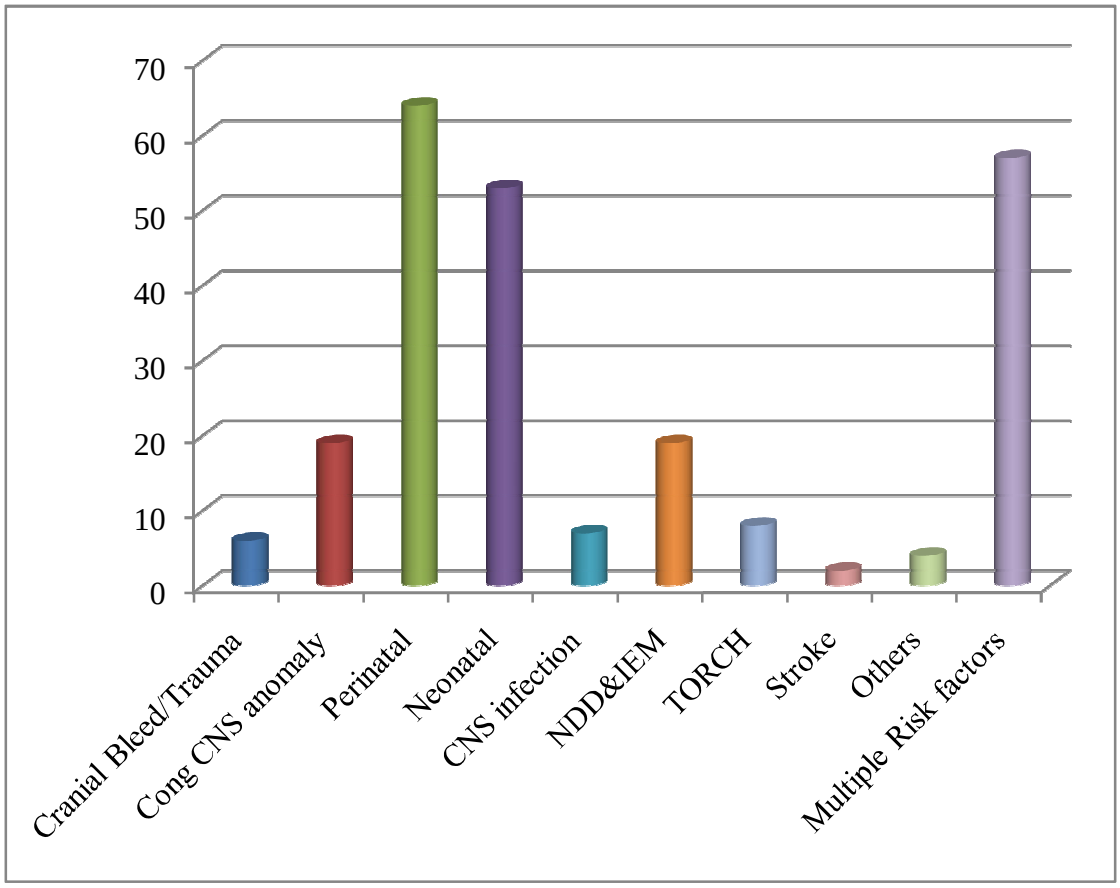
Developmental delay: Among 152 children, 104(68.4%) patients were found to have global developmental delay, with onset prior to starting of AED's.

FEBRILE SEIZURES



Febrile seizures were documented in 55(36.2%) children. p value is < 0.68 which is not within the significant range.

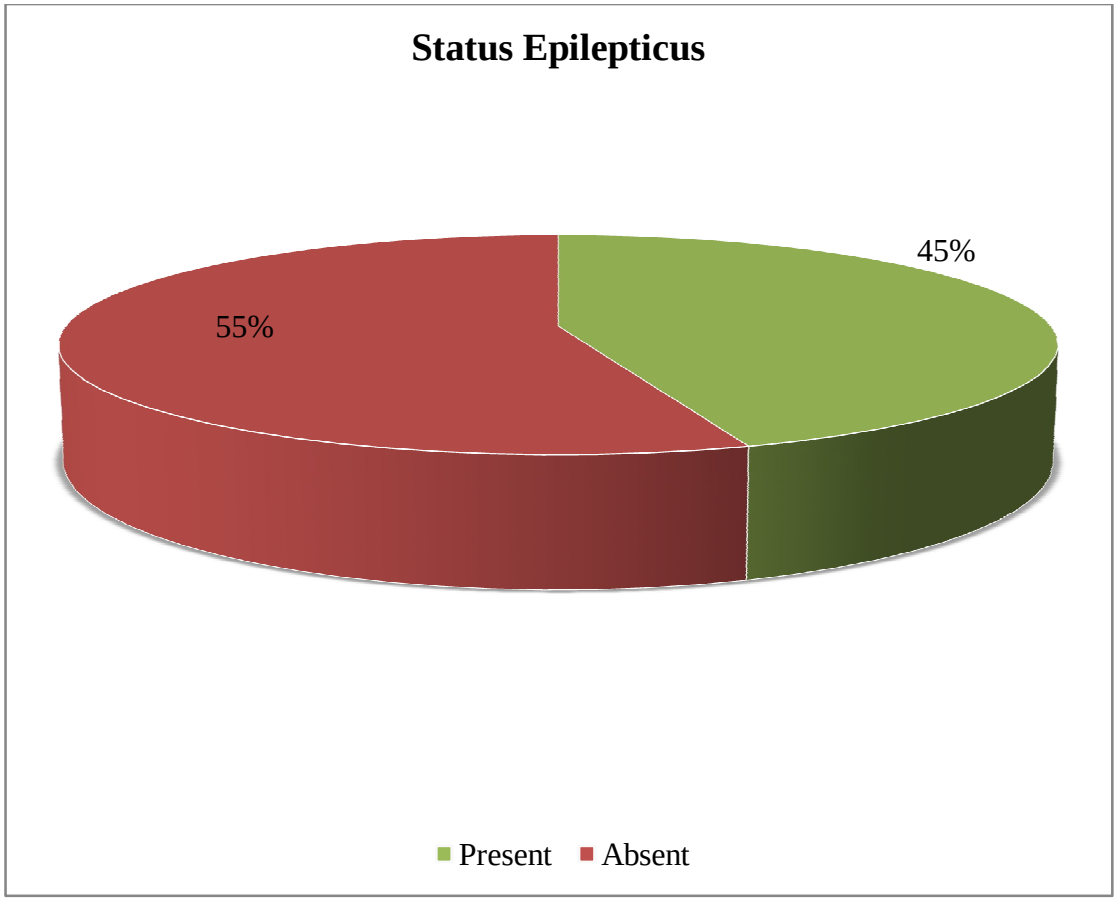
RISK FACTORS



Perinatal injury(64),multiple risk factors(57) neonatal seizures(53) were identified as predominant risk factor. p value also shows the significant association of Perinatal, Neonatal and Multiple risk factor with RE. 23 children had CP due to the perinatal injury, 19 had congenital CNS abnormalities like Tuberous Sclerosis, Neuronal Migration disorder, Struge Weber syndrome, Dandy Walker etc., infection with TORCH was also identified as a risk factor. Inborn

errors of metabolism and Neuro Degenerative disorder (19) like mitochondrial disorders also were important risk factors.

STATUS EPILEPTICUS



Status epilepticus were found in 45.4% of the patients.(69) patients

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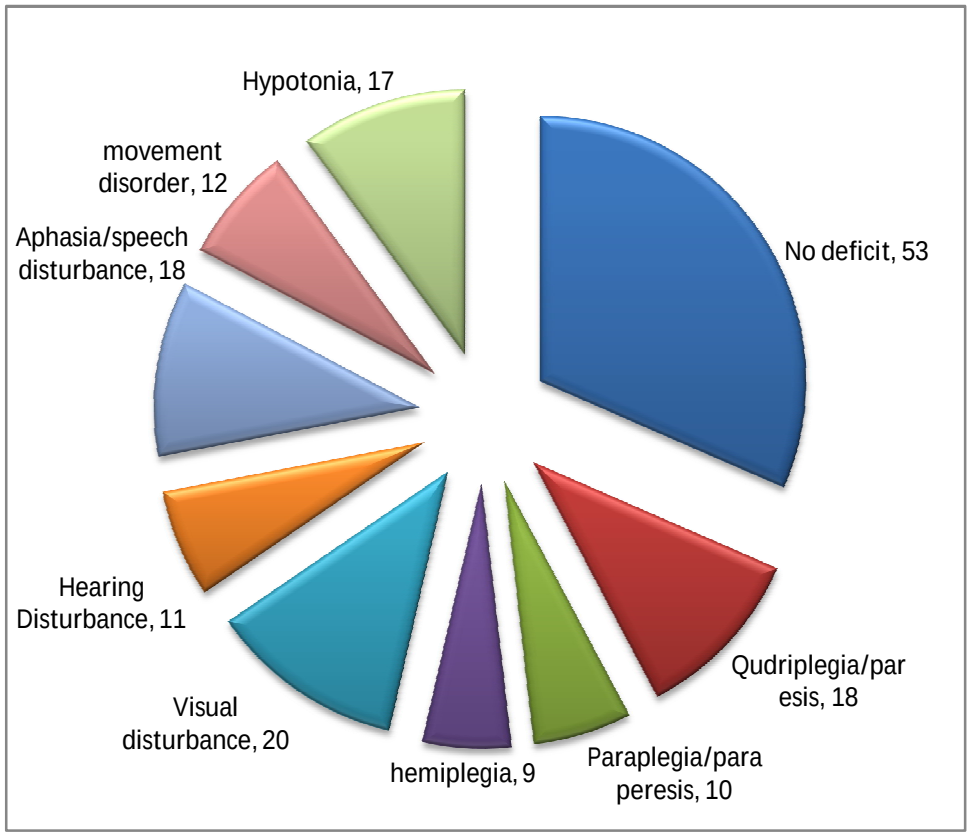
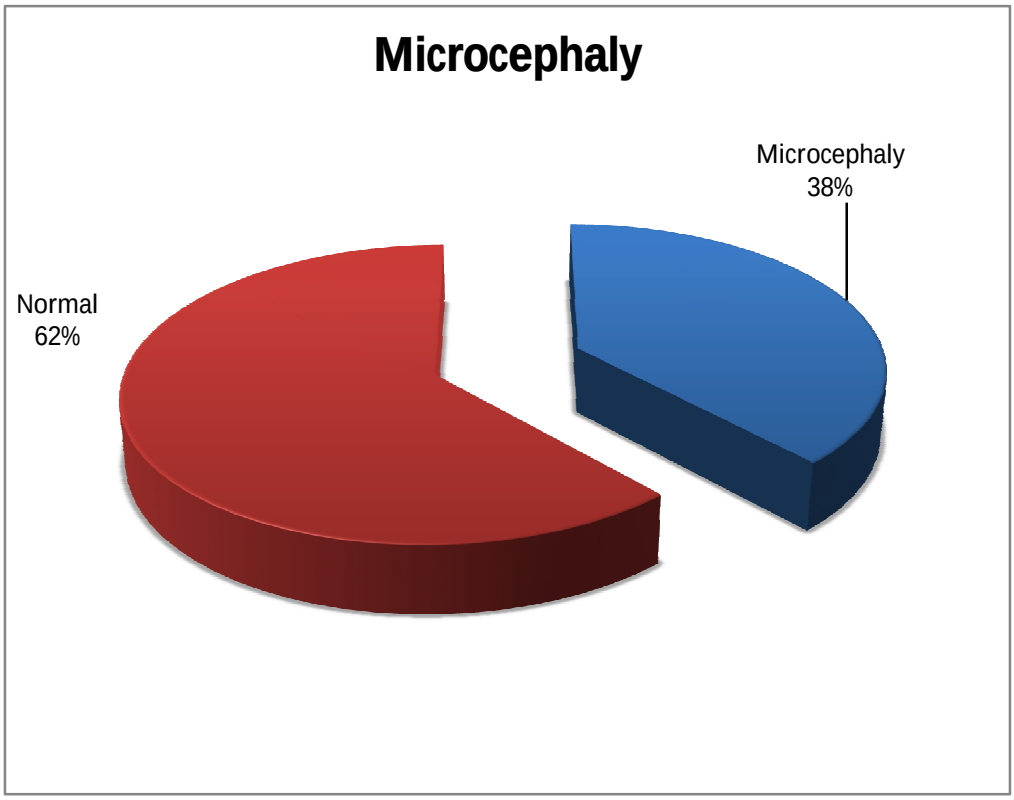
NEURO ABNORMALITY



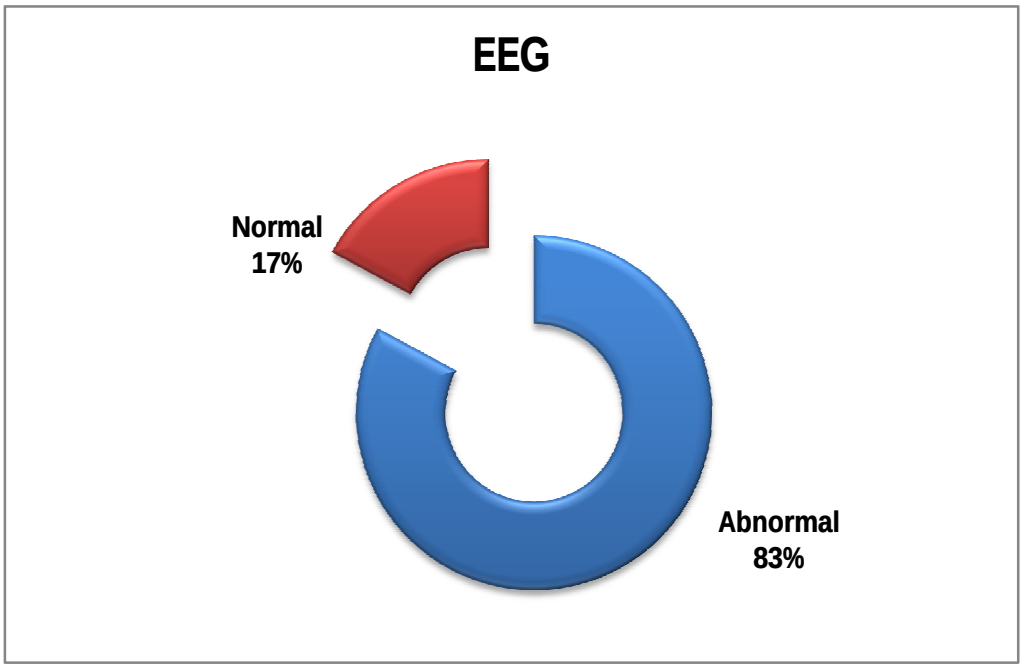
Quadriplegia, Hemiplegia and paraparesis/Paraplegia were associated with cerebral palsy (37). Most had visual disturbance (20), Hearing disturbance(11), Aphasia / Speech disturbance(18), Movement disorder (12),Hypotonia (17).

MICROCEPHALY

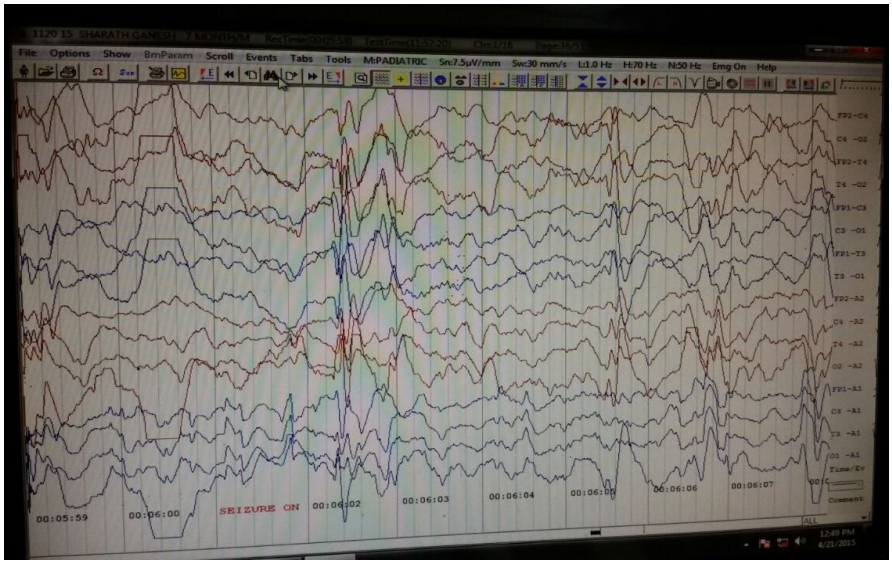


Microcephaly was seen in about 38%, which was associated with cerebral atrophy in the CT scan and MRI reports. p value by Chi square test p was < .001, which shows significant association with RE.

EEG



In this study, EEG was abnormal in 83% of the patients which is a consistent predictor of refractory epilepsy. Bilateral epileptiform discharges was the most common abnormal finding followed by hypsarrythmia pattern. Polyspikes and focal slowing were also present.

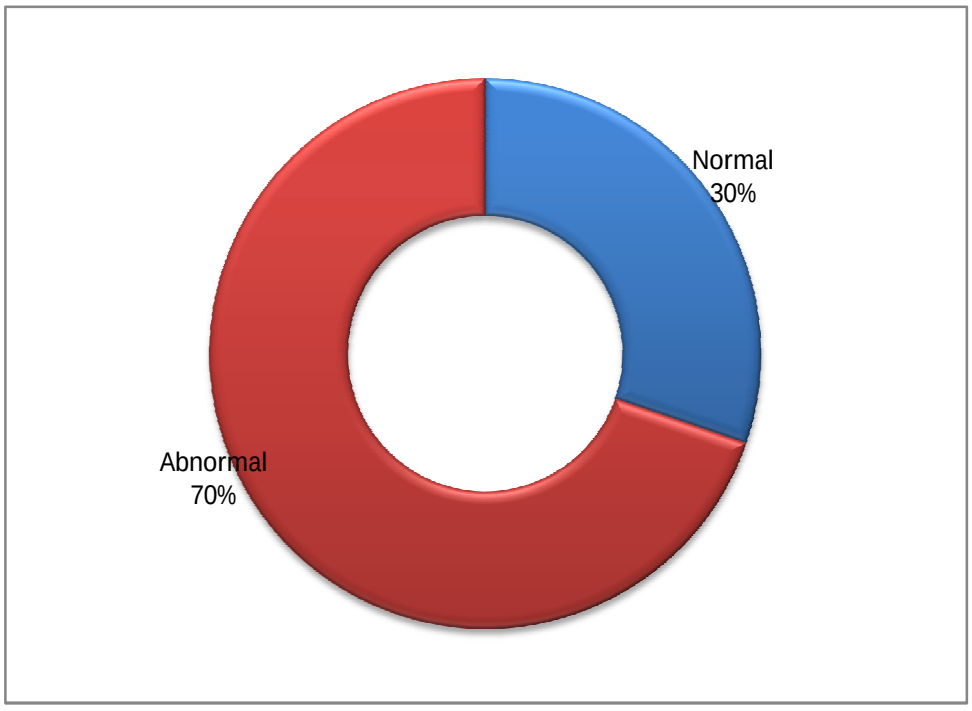


Ictal EEG showing bilateral sharp wave discharges in 7 months old male child with Leigh disease.

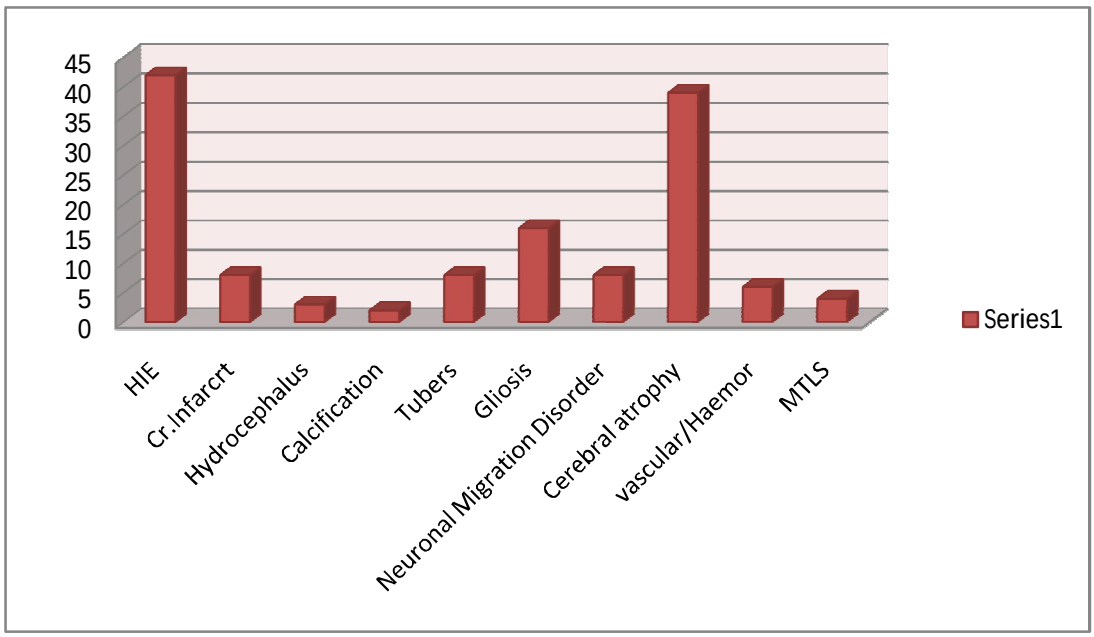
CT Brain

The CT brain scan was normal in 70 children, cerebral atrophy predominating in about 34 patients followed by features of HIE sequelae in 15 and gliosis in 10 and tubers in 6 respectively ,and is associated with perinatal insult and neonatal seizures. Neuronal migration disorder, chronic infarct, tubers of Tuberous sclerosis , mesial Temporal lobe sclerosis was identified by CT brain injury .

MRI

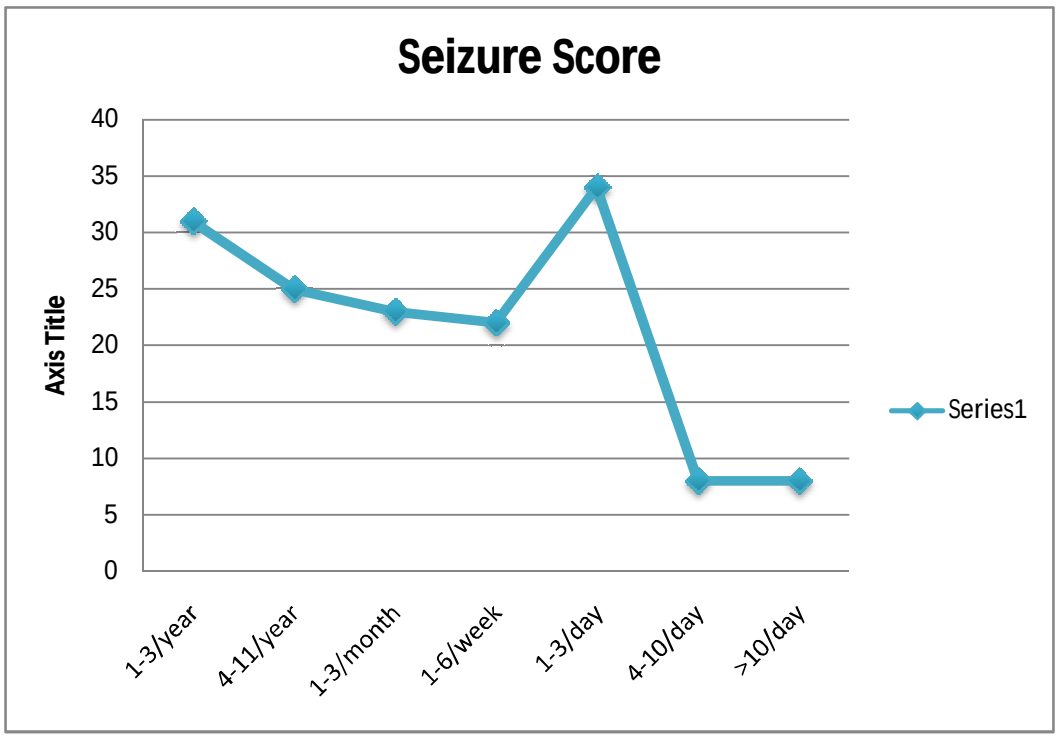


MRI



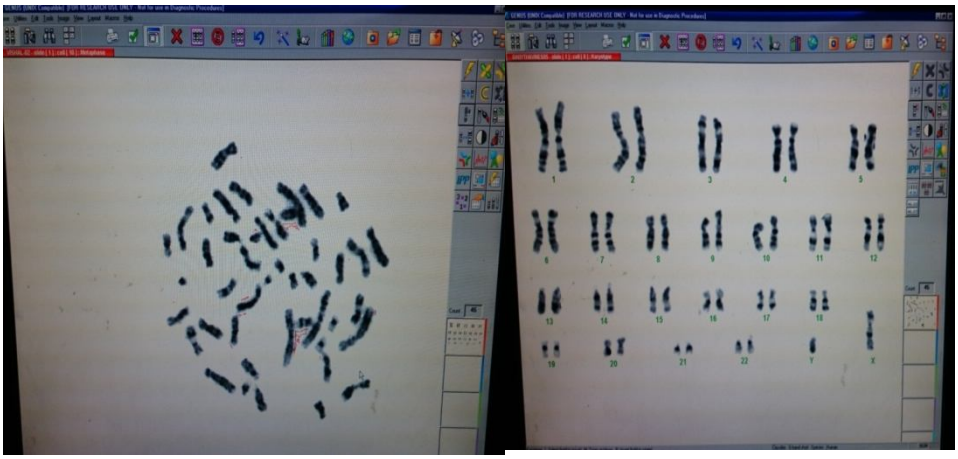
MRI (Imaging abnormality) was documented in 106 children of which 40 had features of HIE, 39 had cerebral atrophy, 8 had cong CNS anomaly, 8 had tubers, 16 had Gliosis, 8 had NMD, 6 had vascular causes. Compared to CTscan MRI is found to be superior in detecting the CNS lesions. While 70 of these had normal CT MRI was normal in only 35 patients. MRI is done as per epilepsy protocol , MRS was done in patients with metabolic disorder.

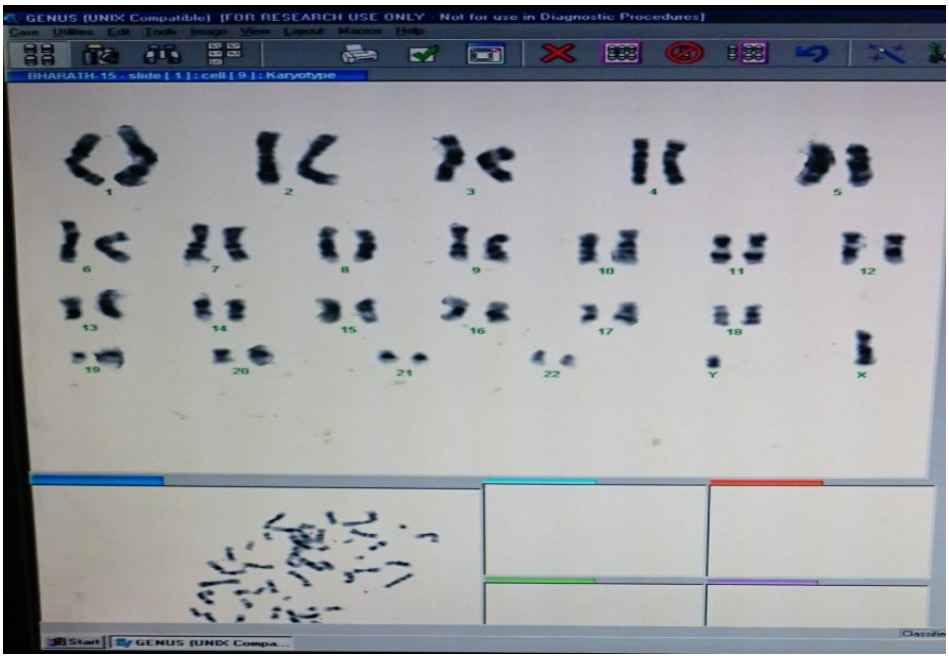
SEIZURE SCORE



Engel's seizure score was also obtained from the questionnaire and this showed the association of high seizure score with RE. Seizure score of 5 and 9 were commonly observed. Seizure score of 9,10,11 were associated with myoclonic and infantile spasms.

KARYOTYPING





Out of 31 patients, who underwent karyotyping, leucocyte for analysis could not be cultured in 3 patients as there was contamination and hence repeated. All the other 28 patients had a normal karyotyping. One had short Y (46XY ah) chromosome which was a normal variant.

SUMMARY

Age and Sex	n-152	Percentage	p value
Male sex	104	67.1	<.001
H/O age of onset <1 year	83	54.6	<.001
Type of the seizures Generalised Myoclonic Infantile spasms	 71 43 17	 46.7 28.3 11.2	 <.001 < .001 <.001
Developmental Delay	107	70.4	<.001
H/O perinatal injury	64	42.1	<.001
Neonatal Seizures	53	34.9	<..001
Multiple Risk factors			<..001
CNS Congenital anomalies	19	12.5	<..001
Degenerative Disorders/IEM	19	12.5	<..001
Microcephaly	58	38.2	< .04
Neuroabnormality	100	68.4	< .001
EEG (abnormal)	129	84.9	<.001
MRI (abnormal)	106	69.7	<001
Seizure score(>1-3/day)	34	22.4	<.001
Behavioral H/o Febrile seizures H/O Status Epilepticus	65 59 65	42.8 38.8 42.8	<.074 <.06 <.25

The summary of the study shows significant p value with many proposed risk factors, Male children are more prone for RE. Infantile

onset of seizures, perinatal insult, neonatal seizures, abnormal neurological examination microcephaly, abnormal EEG, abnormal MRI, and an increased frequency of seizure prior to the treatment were all significantly associated with refractoriness. However in our study, association of status epilepticus, febrile seizures, behavioral abnormality with RE did not show any significant p value.

DISCUSSION

In a devastating disorder like Refractory Epilepsy, the risk factors for intractability have been evaluated in this study. The basic factor that determines the prognosis is the underlying aetiology, identification of the risk factors helps in proper management and prognostication. So it is important to ascertain the type of seizures, localization of the epileptogenic zone, sequence of event, age of onset, sex, perinatal insults, history of status epilepticus etc. Investigations like EEG, MRI, CT scan, TMS, UMS, karyotyping to aid the same. This serves as an important tool in the management of RE.

In our study, the following findings are observed in the results

On analysis of our study, male gender is predominantly affected which is in agreement with Akhondian et. al[1] have but Kwan and Brodie[12/1] have not concurred with the same.

The next risk factor being the age of onset of seizures- predominantly infants(83) and children aged 1-5 years(45) were affected(128/152) similar to Berg *et.*al's study and in accordance with Mohamad Akbar Malik et.al (2005 to 2007).

The third risk factor analyzed based on the seizure semiology was a history of auras. This was present in only 29 patient ,age being the limiting factor. Automatisms and autonomic phenomena were also

assessed in patients, the predominant one being with urinary incontinence followed by ictal vomiting.

Motor phenomena in the form of generalized tonic-clonic seizures was documented in 48 patients, tonic posturing and versive head-turning in about 23 patients, myoclonic in 43 and infantile spasm in 17 patients were the presentation. Jacksonian march was documented in 3 patients. So overall generalized seizures in 71 patients, focal seizures in 68, multiple seizure types in 58 patients. Generalized seizure type had the worst prognosis which was similar to Berg et al study, but the study in the University of Pennsylvania had different results. As per Chi squares or Fisher Exact test, p value shows significant association with generalized seizures.

Myoclonic seizures were present in 43 patients. It had a significant p value of <.01. In 17 patients with Infantile spasms, 15 had TS and 2 had EEG features of hypsarrhythmia without tubers patients. Infantile spasms was associated with RE, p value <.01, as per chi square test. Idiopathic type of seizure was present in 35 patients. Results inferred that seizures due to structural abnormality had the worst prognosis as per Berg et al study which is similar to our study.

The fourth risk factor considered was developmental which is also similar to most other studies,including the one by Vrajesh Udhani et al (Mumbai), Muhammad Akbar malik et al and Berg et al . p value in our

study was significant <0.01,which proves its association with refractory epilepsy.

Out of the 152 children studied, 64 patients had behavioral disturbances, majority (33) had ADHD and another set of patients (31) had hyperactivity, autism and stereotypic behaviors. Children from 6 months to 1 year (27) children were not assessed (17.8 %) and 61 patient had no behavioral symptoms. Prevalence of behavioral disturbances is more in male patients and almost all female child seen with behavioral disorder were associated with ADHD. However the p value < .07 is not significant .in the study by Choudry et al, 43% was associated with ADHD, in our study 42.1% association with behavioral disturbance and out of which 30% is attributed to ADHD. But p value does not show the significant association of behavioral disturbance. The association between ADHD with perinatal injury and neonatal seizures, individually did not show any significance. Prevalence is similar to others studies like Datta et al, done in a tertiary centre in south India in 2005 and Mahi et al done at a tertiary centre in North India 2005.

Febrile seizures were present in 55 patients (36.2%) in our study. The association of febrile seizures with refractoriness is controversial according to Manjari Tripathy et al(3).They observed febrile seizures as an independent factor. Kwan et al showed it as significant on multivariate analysis (3/8).Berg et al proved protective association with febrile

seizures and RE (3/24). Camfield et al study found association of RE with prolonged febrile seizures.(3/25). Febrile seizure is not an associated risk factor according to our study.

Status epilepticus was found in 68 patients (44.7%) which is identical with most of the studies. The patients had received respiratory and admitted for prolonged status in this 68 patients. In Chi square test, p value did not show any significance which is similar to the study by Muhammad Akbar Malik et al 2005-2007

Perinatal insult(64) multiple risk factor(58), neonatal seizures(53) were the major association factors of which ; perinatal insult was the predominant independent risk factor followed by neonatal seizures. Multiple Risk factor also contributed to RE, febrile seizures were not considered as the co existing risk factor. Mohamed Akbar Malik et al found that neonatal seizures were associated with RE. This study was similar to study of "Bebittncourt PR et al,(Epilepsy in the Tropics), Hauser WA et al(Epilepsia 1994)" . Whereas studies in India showed perinatal Injury being more predominating risk factor

Microcephaly seen in 58(76%) of the patients with RE. p value shows significance <.04. It correlates with perinatal insults and cerebral atrophy in MRI. Quadriplegic cerebral palsy has the worst prognosis and the other major associated factor is speech disturbance. Abnormal Neuro Examination was seen in 100 patients with no deficits in 52 patients. A

significant p value of <.01 present shows a strong association with RE. This was accepted by Berg etal study ,Udani et al , M Tripathi et al .

Abnormal EEG was seen in 126 patients who constituted 84%, p value <.001,as accepted by all many other authors. An abnormal EEG was associated with poor outcome.

Seizure Score:

Increased seizure frequency prior to initiation of AEDs is associated with bad prognosis .Multiple seizure frequency is a red flag sign for the treating physician. In our study, Engel's seizure score was also taken as a parameter, to study the burden of RE. In this study, all the patients presented with high seizure score; out of which seizure score >10/day without status epilepticus were associated with cluster of spasms and is also the worst prognosticating factor. p value showed significance value <.01. This is similar to the study of Berg et al.

CONCLUSION

Karyotyping was done in 31 patients out of leukocytes could not be cultered in 3 samples. Out of the remaining 28 patients none of the patients showed any chromosomal abnormality. One male infant had the short Y chromosome, a normal variant. Abnormalities like ring chromosomes, inversion chromosomes, duplication and deletion were looked for. Karyotyping was done for all patients with idiopathic cause of RE with normal phenotype and with dysmorphism.

From this study, the following risk factors are identified as associated with refractoriness. Male sex, infantile onset of seizures in , generalized seizures, multiple seizure types, myoclonic seizures, Infantile spasms, developmental delay, were the bad prognosticating factor Perinatal injury, neonatal seizures, multiple risk factors ,congenital anomalies Tubers sclerosis, Struge weber syndrome, IEM, etc were the main cause of structural and metabolic seizures associated with refractoriness.

Microcephaly, cerebral palsy, focal neurological deficit are the persistent risk factor associated with RE

Children with abnormal EEG, abnormal neuroimaging are particularly associated with higher risk.

High seizure score (increased frequency) prior to the treatment or clusters of seizures carry the bad prognosis

In children the seizure episode , should be evaluated properly and should be treated with appropriate AEDs, this helps the parents to be counseled about the need for continuation of the drugs, associated co-morbid conditions and risks involved with recurrent seizures.

The parents should be appraised of the child's condition and it may help in improving the quality of the life in children with RE.

RECOMMENDATION

The study aims to assess the risk factors associated with the RE. From the study, we have inferred that CNS structural causes produce more refractoriness, gives an idea about the dynamics of the course and relevant individual prognosis.

This study gives an idea about the individual risk factors associated with RE, like male sex, infantile onset of seizures, perinatal insult, neonatal seizures, developmental delay, abnormal neuroimaging abnormal EEG, symptomatic generalized epilepsy, multiple seizure types etc. this helps in prompt treatment and early initiation of treatment , as the longer the treatment worse is the prognosis .

Co-morbid conditions should also be identified and treated along with the RE.

Early identification and the risk factor analysis and dynamics of the disease helps the physician in initiating the appropriate treatment, thereby avoiding the wrong therapy, low dose therapy and infrequent therapy.

Above all identification of the risk factors helps in parental counseling and prepare them for expected outcome.

LIMITATIONS OF THE STUDY

Karyotyping by the conventional method being the first step of the chromosomal analysis can identify only 5-10 mp abnormalities, analysis must be done with the advanced methods like FISH, microarray technique, but the costs limits its use. Antibiotics and other drugs in these children hinder the leukocyte counts and the whole procedure needs to be repeated again.

Being descriptive study, it is a onetime study, needs a follow up study, for the consistent better results. Overall the prevalence of RE could not be studied as our centre caters to Tamilnadu and parts of South India only.

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ABBREVIATIONS

AED’s	-	Anti epileptic drugs
ARS	-	Acute repetitive Seizures
ASS	-	Acute symptomatic seizures
ADHD	-	Attention Deficit Hyperactive Disorder
CT	-	Computed Tomography
DD	-	Developmental Delay
EEG	-	Electroencephalogram
ILAE	-	International League AgainstEpilepsy
MRI	-	Magnetic Resonance Imaging
MRS	-	Magnetic Resonance Spectrometry
NCSE	-	Non Convulsive Status Epilepticus
RE	-	Refractory Epilepsy
SE	-	Status Epilepticus
TS	-	Tuberous Sclerosis

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.G.Thannoli Gowthami
Postgraduate in M.D.(Paediatrics)
Madras Medical College
Chennai – 600 003.

Dear Dr. G.Thannoli Gowthami,

The Institutional Ethics Committee has considered your request and approved your study titled **"Risk Factors for Childhood Refractory Epilepsy in a Tertiary Care Centre" No.39012015.**

The following members of Ethics Committee were present in the meeting held on 20.01.2015 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director , Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
10. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

22/1/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PROFORMA

I Patient Particulars:

OPNO / IPNO:

Name&address : Date of birth :

Age: Sex: Education : Occupation:

Tel.no:

II History: Age of onset duration of c/o

III A Description of the attack (order of appearance of ictal events):

Auras:	CODE	ITEM
0=NO	1=yes	2-Not applicable
Epigastric		
Somatosensory		
Auditory		
Vertiginous		
Olfactory		
Gustatory		
Emotional		
Psychical		

Cephalic (ictal headache)

III B AUTOMATISMS 0=absent.1=present 2-Not applicable

Oroalimentary

Hand

Gestural

Eye blinking

Truncal& body movements

Bicycling/pedaling

Mimetic

Vocalisation

Speech automatism

Ictal speech

Speech arrest

Dysarthria/dysphasia

Gelastic

Dacrystic

III C AUTONOMIC PHENOMENA

0=absent.1=present 2-Not applicable

Ictal vomiting

Tachycardia

Hypertension

Pallor

Piloerection

Urinary incontinence

III D LOSS OF CONSCIOUSNESS (0=absent, 1=present)

Unresponsiveness /Amnesia

III E MOTOR PHENOMENA (0=absent,1=right,2=left 3=generalized))

a. Tonic posturing

b. Dystonic posturing

c. Versive head turning

d. atonic

e. Generalisation

f. Jacksonian March

g. Clonic

h. Nonversive head turning

III F POST-ICTAL PHENOMENA Dysphasia/aphasia

(0=absent,1=present)

Duration(mm/ss)

Amnesia (0=absent,1=present)

Todd,s paralysis (0=absent,1=present)

Psychoses

III G MYOCLONIC JERKS : face/limbs/generalised

III H INFANTILE SPASMS

III I Predicting factors for seizures: 0-absent 1-Present

1. Sleep deprivation
2. Sudden awakening provoked /Spontaneous
3. Fatigue and exercise
4. fever
5. Hyperventilation/emotional

III J Triggering factors 0-absent 1-Present

1. Visual stimuli
2. Auditory stimuli

3. Somatosensory stimuli
4. Reading
5. Music listening
6. Eating
7. Cognitive effort
8. Self-induced

III K Timing of seizures:

1. Nocturnal
2. Diurnal
3. Anytime

IV Behavioral disturbances & Neuropsychological Evaluation:

V Birth & Developmental History: 0-normal 1-delay

Milestones a. motor

b. IQ/DQ

c. Mental

d. Social

VI Past & Personal history:

H/O Age of first Unprovoked seizures.

Febrile seizures 0-absent 1-present

VII Risk factors of epilepsy: Age at which it occurred: --------

0. idiopathic
1. Cranial trauma
2. Congenital CNS abnormalities
3. Perinatal birth trauma
4. Neonatal seizures
5. Stroke
6. CNS infection(name)

   a.Viral b. Fungal c. Pyogenic d. Tuberculous e. Parasitic (cysticercosis) f. HIV Others (mention)
7. Degenerative brain disease
8. Cerebral palsy
9. MS
10. Drugs/Toxins (mention)
11. H/o febrile seizures
12. H/o endocrine
13. CNS malignancies (mention)
14. Inherited metabolic disorders
15. Chromosomal abnormalities
16. Metabolic
    Hypoglycemia, Hyperglycemia, Hyponatremia, Hypernatremia, Hypocalcemia, Hypomagnesium
17. H/O status epilepticus: NO of attacks and Age at which it occured
18. H/O > 2years of remission of seizures at any time (mention)

VIII Family History:

Family h/o epilepsy : 1-yes/0-no

With pedigree chart : 0-Nonconsanguinous (1^o 2^o 3^o)

Siblings : 0-no 1-yes

IX Neurological examination:

0- No deficit

1- Quadrplegia

2- Paraplegia

3- Hemiplegia

4- Visual disturbance

5- Hearing impairment

6- Aphasia

7- Movement disorder

8- Microcephaly

X Investigations:

Imaging:

CTSCANBrain0-Normal 1-HIE 2-Chronic Infarct 3-Hydrocephalus

5-Calcification 6-Tubers 7-Gliosis 8-Neuronal migration disorders

9-Cerebral atrophy 10-Others

MRI Brain

0- Normal

1- HIE

2- Chronic Infarct

3- Hydrocephalus

5- Calcification

6- Tubers

7- Gliosis

8- Neuronal migration disorders (LissencephalySchizencephaly subcortical

Heterotropia Bilateral perisylvianpolymicrogyria Corpus callosal agenesis Prosencephalic cyst)

9- Cerebral atrophy

10- Vascular Malformations

11- Mesial temporal lobe sclerosis

12- Others

MRS

XI TMS

UMS

ECG

ECHO

XII TORCH

EEG:

Seizure semiology:

Karyotyping

XIII Treatment Details and Follow up:

AEDs tried so far:

1- DPH,

2- CBZ

3- VPA

4- PB

5- Clobazam

6- Clonazepam

7- Leviteracetam

8- others (specify)

The AED patient found most suitable & acceptable ----------

XIV Seizure Scoring System:

Seizure frequency	Score
Seizure free, off the AED	0
Seizure free, need for AED unknown	1
Seizure free, requires AED to remain so	2
Non disabling simple partial seizures	3
Non disabling nocturnal seizures only	4
1-3per year	5
4-11 per year	6
1-3 per month	7
1-6 per week	8
1-3 per day	9
4-10 per day	10
>10 per day but not status epilepticus	11
Status epilepticus without barbiturate coma	12

Information to Participants

Title: "Risk factors for childhood refractory epilepsy in a tertiary care center, Chennai.

Principal Investigator : **DR.G.Thannoli Gowthami**

Name of Participant :
Age : Sex :

Name of the Institution : Institute of Child Health & Hospital for Children
Neurology OPD,
Madras Medical College, Chennai.

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Childhood refractory epilepsy is a common disorder characterized by recurrent attacks of seizures (fits). It usually presents as different types of seizures. early identification and treatment helps in improving prognosis and helps in parents counseling.

We have obtained permission from the Institutional Ethics Committee.

The study design

Children fulfilling the inclusion criteria will be included in the study after getting consent. All patients with refractory seizures are assessed for risk factors of refractory childhood epilepsy, karyotyping analysis in refractoriness for the patients with the normal phenotype with cognitive and behavioural problems with seizures.

Study Procedures

The study involves evaluation of children with refractor, epilepsy which includes standard questionnaire, physical examination and certain investigations like basic blood investigations, EEG, and neuro imaging (CT / MRI Brain). You will be required to visit the hospital _____ number of times during the study. A diligent karyotyping to be performed in these patients who presented to us with refractory epilepsy with normal phenotype.

At each visit, the study physician will examine you. If applicable some selected patients will undergo Karyotyping examination they collecting 1ml of blood. Blood collection involves prick with a needle and syringe. These tests are essential to monitor the outcome of the disease and helpful in parental counselling.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator

Date

Signature of Participant

Date

INFORMED CONSENT FORM

Title: ***Risk Factors for Childhood Refractory Epilepsy in a Tertiary Care Center,*** **Chennai.**

Name of the Investigator: **DR.G.Thannoli Gowthami**

Name of the Participant:

Age : Sex:

Name of the Institution: Institute of Child Health & Hospital for Children
Neuro OPD, Madras Medical College, Chennai.

Hospital No.: Blood Sample No:

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have informed the investigator of all the treatments I am taking or have taken in the past months/years including any native (alternative) treatments.
6. I have been advised about the risks associated with my participation in the study.*
7. I agree to cooperate with the investigator and I will inform him /her immediately if I suffer unusual symptoms. *
8. I have not participated in any research study within the past _____ month(s). *
9. I have not donated blood within the past _____ months. (Add if the study involves extensive blood sampling). *
10. I am aware of the fact that I can opt out of the study at any time without having to give any reasoned this will not affect my future treatment in this hospital. *
11. I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent. *
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC if required.
13. I understand that my identity will be kept confidential if my data are publicly presented.
14. I have had my questions answered to my satisfaction.
15. I consent voluntarily to participate in the research/study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

For children being enrolled in research

1. Name and signature / thumb impression of the participants parent (s)/ guardian (or legal representative)

   Name _____ Signature_____ Date_____

2. Name and Signature of impartial witness (required for illiterate parents):

   Name _____ Signature_____ Date_____

   Address and contact number of the impartial witness:

3. Name and Signature of the investigator or his representative obtaining consent:

   Name _____ Signature_____ Date_____

For observational studies or those in which patients tissue, body fluids are collected for any kind of analysis, **points 6,7,8,9,10,11** may be excluded in such cases.

தகவல் படிவம்

ஆராய்ச்சி தலைப்பு: வலிப்பு நோய் பாதித்த குழந்தைகளில் மருத்துவ சிகிச்சையினால் கட்டுப்படுத்த முடியாத காரணங்களைப் பற்றி (Risk Factors) ஆய்வு செய்தல்.

இடம்: அரசு குழந்தைகள் நல மருத்துவமனை, எழும்பூர், சென்னை-8.

ஆய்வாளரின் பெயர்: மரு.கௌ.தண்ணொளி கௌதமி
எம்.டி (குழந்தைகள் நலம், இரண்டாமாண்டு)

தேதி:

உள்/வெளி நோயாளி எண்:

குழந்தையின் பெயர்: ஆராய்ச்சி சேர்க்கை எண்:

த/பெயர் :

வயது :

பாலினம் :

தங்கள் குழந்தையும் இந்த ஆய்வில் பங்குபெற கேட்டுக்கொள்கிறோம்.

1) வலிப்பு நோய் பாதித்த குழந்தைகளில் மருத்துவ சிகிச்சையினால் கட்டுப்படுத்த முடியாத காரணங்களைப் பற்றி (Risk Factors) ஆய்வு செய்தலே இந்த ஆய்வின் நோக்கம்.

2) சில குழந்தைகளுக்கு மரபணு (Karyo Typing) சோதனை இரத்தத்தின் மூலம் செய்து மருத்துவ சிகிச்சைக்கு கட்டுப்படாத காரணத்தை கண்டறிதல்.

3) இந்த ஆய்வின் முடிவுகள் பற்றி உங்களுக்கு தெரிவிக்கப்படும்.

4) இந்த ஆய்வின் மூலம் கண்டறியப்படும் முடிவுகள் உங்கள் குழந்தையின் சிகிச்சைக்கு மிகவும் உதவியா இருக்கும்.

5) இந்த ஆய்வில் கலந்துகொள்வதன் மூலம் என் குழந்தையிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்ட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்துகொள்ளலாம் என சம்மதிக்கிறேன்.

6) உங்கள் குழந்தையை பற்றிய விபரங்கள் யாருக்கும் தெரிவிக்காமல் பாதுகாக்கப்படும்.

7) இந்த ஆய்வில் பங்குபெறுவது உங்கள் தனிப்பட்ட விருப்பம் ஆகும். நீங்கள் இந்த ஆய்விலிருந்து எப்பொழுது வேண்டுமானாலும் விலகிக்கொள்ளலாம். அவ்வாறு விலகுவாதல் குழந்தையின் சிகிச்சையில் எந்தவித பாதிப்பும் ஏற்படாது.

8) ஆய்வாளர் இந்த ஆய்வில் எனது பங்களிப்பை எந்த நேரத்திலும் எந்த காரணத்திற்காகவும், எந்தவித ஒப்புதல் இல்லாமலும் நிறுத்திக்கொள்ளலாம் எனவும் தெரிந்துகொண்டேன்.

9) இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், ஆய்வாளரை தொடர்புகொள்ளலாம்.

இச்சுய தகவல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன். இச்சுய படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்துகொண்டேன்.

பங்கேற்பாளர்

பங்கேற்பாளருடைய பெயர் மற்றும் கையொப்பம்/கைரேகை (அல்லது சட்ட ரீதியான பிரதிநிதி-பங்கேற்பாளர் செயல்திறமையற்றவராக இருந்தால்/17வயதிற்குகீழ் உள்ளவர்களுக்கு - பெற்றோர்/பாதுகாவலர்)

.....	.....	.....
பெயர்	கையொப்பம்/கைரேகை	தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் பெயர் மற்றும் கையொப்பம் (படிப்பறிவு இல்லாத மக்களுக்கு)

.....	.....	.....
பெயர்	கையொப்பம்/கைரேகை	தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் முகவரி மற்றும் தொலைபேசி எண்

.....	.....	.....
ஆராய்ச்சியாளரின் பெயர்	கையொப்பம்	தேதி

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு: வலிப்பு நோய் பாதித்த குழந்தைகளில் மருத்துவ சிகிச்சையினால் கட்டுப்படுத்த முடியாத காரணங்களைப் பற்றி (Risk Factors) ஆய்வு செய்தல்.

இடம் : அரசு குழந்தை நல மருத்துவமனை, எழும்பூர், சென்னை-8.

குழந்தையின் பெயர் :

த/பெயர் : தேதி :

வயது : உள்/வெளி நோயாளி எண் :

பாலினம் : ஆராய்ச்சி சேர்க்கை எண் :

..... என்பவராகிய நான் இந்த ஆய்வின் விவரங்களை படித்து தெரிந்துகொண்டேன் (அல்லது) எனக்கு படித்து காண்பிக்கப்பட்டது. அதன் நோக்கங்களும் முறையாக அறிந்துகொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் பங்குகொள்ள சம்மதிக்கிறேன்.

1. இந்த ஒப்புதல் படிவத்தை நான் படித்து புரிந்துகொண்டேன்.
2. இச் சுய ஒப்புதல் படிவத்தை பற்றி எனக்கு விளக்கப்பட்டது.
3. இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது.
4. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை பற்றி அறிந்து கொண்டேன்.
5. தற்போது என் குழந்தை எடுத்துக்கொண்டிருக்கும் (அல்லது) முன்பு எடுத்துக்கொண்ட மருத்துவ விவரங்களை ஆய்வாளருக்கு தெரிவித்துள்ளேன்.
6. இந்த ஆய்வின் என் குழந்தையின் பங்களிப்பினால் குழந்தைக்கு எந்த பின்விளைவுகளும் ஏற்படாது.
7. இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.
8. ஆய்வாளர் இந்த ஆய்வில் என் குழந்தையின் பங்களிப்பை எந்த நேரத்திலும் எந்த காரணத்திற்காகவும், எந்தவித ஒப்புதல் இல்லாமலும் நிறுத்திக்கொள்ளலாம் எனவும் தெரிந்துகொண்டேன்.
9. இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என் குழந்தையிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்துகொள்ளலாம் என சம்மதிக்கிறேன்.
10. இந்த ஆய்வின் முடிவுகளை வெளியிடும்போது என் குழந்தையின் பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்துகொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.
11. எனது எல்லா கேள்விகளுக்கும் திருப்திகரமாக பதிலளிக்கப்பட்டது.

12. இந்த ஆராய்ச்சியில் பங்களிக்க வேண்டுமென முடிவு செய்துள்ளேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்புகொள்ள வேண்டும் என அறிந்துகொண்டேன்.

என் குழந்தைக்கு இரத்த பரிசோதனை செய்ய அனுமதி தருகிறேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்துகொண்டேன்.

பங்கேற்பாளர்

பங்கேற்பாளருடைய பெயர் மற்றும் கையொப்பம்/கைரேகை (அல்லது சட்ட ரீதியான பிரதிநிதி - பங்கேற்பாளர் செயல்திறமையற்றவராக இருந்தால் / 17வயதிற்குகீழ் உள்ளவர்களுக்கு - பெற்றோர் / பாதுகாவலர்)

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பெயர் கையொப்பம்/கைரேகை தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் பெயர் மற்றும் கையொப்பம் (படிப்பறிவு இல்லாத மக்களுக்கு)

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பெயர் கையொப்பம்/கைரேகை தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் முகவரி மற்றும் தொலைபேசி எண்

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ஆராய்ச்சியாளரின் பெயர் கையொப்பம் தேதி

S.No	Patient Id	Age &	sex	Age of onset	Auras	Automat	Auto nomic	LOC	Motor1	Motor2	Motor3	Motor4	Motor5	Motor6	Motor7	Postictal Events	Myoclonic	Infantile spasms	Predictin factors	Predictin factors. 1	Predictin factors.2	Predictin factors .3	Predictin factors.4	Predictin factors.5	Timing of seizure1	Timing of seizure2	Timing of seizure3	Timing of seizure4	Beha vioural	DD	H/o Febrile	Risk Factors1	Risk Factors2
1	1-TN	9	M	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0							1			0		0	0	
2	2-BI	6	F	0	0	0	0	1	0	0	0	0	3	0	0	0	0	0	0									1	1MR		1	1	
3	3-PN	1	M	0	0	0	0	1							1	0	0	0	0							1			0		1	1	
4	4-SK	3	M	0	0	0	0	1	3							0	0	0	0									1	0		1	1	
5	5-SR	9	M	2	0	1	1	1					3			0	0	0						1	1				1ADHD		1	0	
6	6-UD	9	M	2	0/0	0	0	1							3	1	0	0	0							1			0		0	0	
7	7/DH	9/12m	M	0	2	0	0	1					3			1	1	0	0									1	2		1	1	
8	8/VD	8	M	1	0	0	1	1					3			1	1	0	0						1				1ADHD		1	0	
9	9DE	7/12m	M	0	2	0	0	1	3							1	1	1	0							1			0		1	0	
10	10SH	2	F	0	2	0	0	1					3			1	0	0	0						1				0		0	1	
11	11SA	7	M	1	0	0	1	1					3			1	1	0	0						1				1ADHD		1	0	
12	12BH	1.7	M	0	1	0	0	1	0							0	0	1			1							1	0		0	0	
13	13SRY	10	M	1	0	1	0	1	3							1	0	0				1				1			0		1	0	
14	14YU	11	M	2	0	0	0	1						3		1	0	0				1						1	0		0	1	0
15	15DH	2.3	F	0	2	0	0	1	3							1	0	0					1	1				1	0		1	0	1
16	16PR	1	M	0	0	0	0	0	0							0	0	1										1	0		1	0	
17	17My	2	F	1	2	0	0	0	1		1					1	0	0	0						0				1		0	0	
18	18LO	5	M	1	2	0	0	0		1						0	0	0	0										0		0	1	0
19	19PL	5	M	1	2	0	1	1					3			0	0	0		1						1			0		1	1	
20	20AS	6	M	2	0	0	0	1	3		3					1	0	0		1		1			1				0		0	0	1
21	21BU	9	M	0	2	0	0	0	2							0	1	0	0							1			0		1	0	
22	22HE	1.6	M	0	2	0	0	1					3			1	0	1	0							1			0		1	1	
23	23Go	2	F	0	2	0	0	1	3		3					1	0	0		1								1	0		1	0	0
24	24Ja	3	M	1	1	0	0	1	0							0	1	0		1						1			0		0	1	0
25	25Log	12	M	2	0	0	0	1	3		3					1	0	0		1		1						1	1ADHD		1	1	7+4
26	26KU	12	M	1	1	1	0	1						3		1	0	0		1						1			1ADHD		0	1	0	
27	27San	2.8	F	0	2	0	0	0	0							0	1	0	0									1	0		0	1	0
28	28Pb	6	M	1	0	0	0	1			3					0	1	0	0									1	0		1	0	
29	29Mu	9	M	1	0	0	0	1				1				1	0	0	0							1			1		1	0	
30	30Sk	3	M	0	2	0	0	1					3			1	0	0					1					1	1		1	0	
31	31Uv	9/12m	F	0	2	0	0	1	0							0	1	0	0									1	0		1	0	0
32	32La	9/12m	F	0	2	0	1	1	0							1	1	0	0						1				0		1	0	
33	33Ju	1	F	0	2	0	0	1			1					1	0	0		1			1					1	0		1	1	1
34	34Ka	6.5	F	2	0	0	0	1			2					1	0	0		1				1				1	1		0	1	0
35	35Sn	10	F	1	1	1	1	1			2					1	0	0	0							1			1		0	0	
36	36Bav	2	M	0	2	0	0	1					3			1	0	0					1					1	0		0	1	
37	37Mn	7	F	0		0	0	0					3			1	0	0	0									1	0		1	0	1
38	38/DE	11	F	1	0	1	0	1			2					1	0	0				1			1				1		4	0	0
39	39/Ka	7	M	1	0	1	0	1			3					1	1	0	0						1				0		0	0	1
40	40Jp	2	F	1	2		1	1			2		3			1	0	0	0							1			0		0	0	0
41	41Tr	1.1	M	0	2		0	1					3			1	0	0	0						1				0		0	1	1
42	42El	9	M	2	0	1	1	1					3		3	1	0	0	0							1				1		1	0	1
43	43He	6	M	0	0		0	1					3			1	0	0	0							1			1		0	0	
44	44Vis	10	M	2	1	1	1	1	2							1	0	0					1		1				1		1	0	0
45	45SA	10/12m	M	0	0		0	0	0							0	1	0	0							1			0		1	0	
46	46MD	7	M	2	0		0	1			3					1	0	0	0						1				1		1	0	
47	47SA	1	F	0	0		0	0	0							0	0	1			2					1			0		1	0	2	1
48	48Je	3.6	F	0	2		1	1					3			1	1	0	0							1			0		1	0	2	1
49	49YM	9	F	2	2		1	1					3			1	0	0	0							1			1		1	1		
50	50Da	1	M	0	0		0	0	0							0	0	1			1					1			0	1d		0		1
51	51PO	5	F	2	0		0	1					3			1	0	0					1					1	1		1	1	
52	52MN	12	M	1	0		0	1					3			1	0	0	0							1			0		0	0	1	
53	53HE	6	M	0	0		0	1					3			1	0	0	0							1			1		0	0	0	
54	54SV	7	M	1	1	1	1	1	3							1	0	0		1		1			1				0		0	0	0	
55	55YG	6/12m	M	0	2		1	1					3			1	1	0	0							1			0		1	0		
56	56ABI	4.6	F	1	0		0	1			1					0	1	0						1					1		1	0		
57	57GA	10	F	2	0		0	0				1				0	1	0						1		1			1		1	0	0	
58	58RK	1	M	0	0	1	0	0	0							0	1	0	0									1	0		1	0	
59	59 SA	1.6	M	0	0		1	1	2		2					1	0	0			1							1	1		1	0	1
60	60 SS	4	F	0	0		0	1					3			1	0	0	0									1	0		1	1	0
61	61MN	3.6	M	1	2	1	0	1	1							1	0	0	0							1			0		1	0		
62	62CD	5	M	0	0		1	1				1				1	0	0	0									1	1		1	0		1
63	63PN	9	F	1	0		0	1					3			1	0	0	0									1	1		1	1	0	
64	64FA	2.8	F	0	0		0	1	2		2					1	0	0	0									1	1		1	0		
65	65KI	1.6	F	0	0		0	1					3			1	1	0	0									1	0		1	1		
66	66NT	2.6	M	0	2	1	1	1	1							1	0	0					1			1			1		1	1	0	
67	67DG	7	F	1	0		1	1					3			1	0	0	0									1	1ADHD		1	1		
68	68MT	7	M	0	1	1	0	1			2					1	1	0		1		1						1	1ADHD		1	0		
69	69KK	10	M	2	1	1	0	0	2							0	0	0	0									1	1ADHD		0	0	0	
70	70LD	5	M	1	1		0	1	1						1	0	0	0				1	1					1	0		0	1		
71	71RS	3.6	F	0	2		1	0					3			0	1	0				1			1				0		1	0		
72	72CD	5	M	0	0	1	1	0				1				0	0	0					1			1			1	0		1		1
73	73LN	3	M	1	0		1	1	3							1	0	0	0						1				0		0	0		
74	74OO	2	F	0	0	1	0	1	2		2		3			1	0	0					1			1			1ADHD		0	1	0	
75	75BV	10/12m	F	0	0	1	0	0	0							0	1	0	0									1	1		1	1		
76	76VG	5	F	1	0	1	0	1	2						2	1	1	0			1				1				0		1	1		
77	77SR	7/12m	M	0	0		0	1	0							0	1	0	0									1	0		0	1		
78	78YZ	10/12m	F	0	0		0	1					3			1	0	0	0									1	0		0	1	0	
79	79AR	9	M	2	0		0	0					3			0	0	0	0									1	1		0	0	0	
80	80PV	3	M	0	0		0	1					3			1	0	0	0									1	1		1	1		
81	81AS	5	M	1	0		0	1	0							1	1	0			1							1	1ADHD		1	1		1
82	82SH	5	M	1	0		0	0	0							0	1	0	0									1	0		1	0		
83	83CP	11	M	0	0	1	1	1	2						2	1	0	0	0						1				1ADHD		1	1		
84	84IY	12	M	2	11/0		1	1	1						1	1	0	0	0						1				0		0	0	0	
85	85SA	6	M	0	2	1	0	1	2							0	1	0	0						1				0		1	0		
86	86GAY	3	F	1	0		0	1	0							0	1	0	0							1			1AU		1	0		
87	87RAG	3	M	1	0		0	0				1				0	0	0			1	1				1			1		0	0		
88	88GK	7/12m	M	0	0		2	0	0							0	0	1			1					1			1		1	0		
89	89JAY	7	F	1	0		0	1							2	1	0	0						1	1				0		1	0		

S.No	Patient Id	Age &	sex	Age of onset	Auras	Automat	Auto nomic	LOC	Motor1	Motor2	Motor3	Motor4	Motor5	Motor6	Motor7	Posticta Events	Myoclonic	Infantile spasms	Predictin factors	Predictin factors. 1	Predictin factors.2	Predictin factors .3	Predictin factors.4	Predictin factors.5	Timing of seizure1	Timing of seizure2	Timing of seizure3	Timing of seizure4	Beha viioural	DD	H/o Febrile	Risk Factors1	Risk Factors2
90	90D	6/12m	F	0	0		0	1			1					0	1	0	0									1	2	1	0		
91	91PV	1.3	F	0	0		0	0	0							0	0	1	0									1	0	1	0		
92	92ES	5	M	1	1		0	1	2							1	0	0		1			1					1	0	0	1		
93	93Ar	1	F	0	2		2	1							2	1	0	0	0									1	0	1	0	0	
94	94/KR	9	M	2	0		0	0		2						1	0	0	0						0				4	1	1		
95	95pr	6	M	1	0	1	0	1	1							1	0	0				1		1	1				1ADHD	1	0	3	
96	96IR	4	M	1	2		0	1					3			1	0	0	0									1	0	0	0	0	
97	97ML	2	F	0	0		0	1	0							1	1	0					1					1	0	1	1		
98	98kk	11	M	0	0		0	1			2					0	0	0		1								1	1ADHD	1	1		
99	99MR	2	M	0	2		0	0	0							0	0	1			1							1	0	1	0		
100	100/EZ	8	F	1	2		0	0	0							0	1	0						1	1				0	1	1		
101	101/A	6/12m	F	0	2		0	1					3			1	0	1			1							1	2	1	0	0	
102	102Ay	9	M	2	0		0	1	3							0	0	0			1							1	1AU	1	0	0	
103	103TM	6	M	1	0		0	1					3			0	0	0	0							1			1ADHD	1	0		
104	104SM	1	M	0	2		0	0	0							0	1	0			1				1				0	1	0		
105	105MS	3	M	2	0		0	0	0							0	0	1			1							1	0	1	0		
106	106Pr	4.6	F	2	0		1	1	3							1	0	0	0									1	0	1	1		1
107	107EP	6	M	0	0		0	0	0							0	0	1			1							1	1ADHD	1	0		
108	108ER	3	M	0	2		0	1					3			1	0	0	0									1	0	1	0		
109	109MD	9	M	0	2		0	1					3			0	0	0					1						1	0	1	0		1
110	110VN	6/12m	M	0	2		0	0	0							0	1	0	0									1	0	1	0		
111	111KA	5	M	0	2	1	0	1					3			0	0	0		1								1	0	1	0		
112	112GS	8	M	0	0		0	1	0							0	1	0	0									1	0	1	1		
113	113Ka	3	F	1	0		0	1	0							0	1	0	0									1	1ADHD	0	0	1	
114	114LK	6	M	0	0		0	1	3							0	0	0	0									1	0	1	0		1
115	115Bj	11	F	0	0		1	1					3			1	0	0	0									1	1	1	0		
116	116Sr	7	F	2	0		0	1			2					1	0	0	0							1			1	0	0		
117	117Pj	11/12m	M	0	2		0	0	0							0	0	1			1					1			0	1	1		1
118	118Ns	8	M	1	0		0	1	0							0	1	0			1							1	1ADHD	1	1		
119	119VG	11	M	2	0		0	1							1	1	0	0						1				1	0	0	0	0	
120	120Gp	3	M	0	0		0	1	0							1	1	0	0									1	0	1	1		
121	121Tr	9	M	1	1	1	1	1							1	1	0	0	0							1		1	0	0	0	0	
122	122Yr	7	F	1	2		0	1					3			1	0	0		1								1	1ADHD	1	0		
123	123Ib	2	M	0	2		0	1					3			1	0	0					1					1	1ADHD	0	1	0	
124	124Ch	11	M	0	0		0	1							1	1	0	0	0						1				0	0	0	0	
125	125Pr	4.6	M	1	2		1	1	3							1	0	0	0									1	0	1	1		
126	126Pe	4.9	F	1	0		0	0			2					1	0	0	0									1	1ADHD	1	0	0	
127	127Jo	12	M	0	0		0	1							1	1	0	0	0									1	1	1	0		
128	128RK	12	M	2	1		0	1					3			1	0	0			1							1	1	1	0		
129	129PR	1	M	0	0		0	0	0							0	1	1	0									1	0	1	0		
130	130HR	2	F	0	2		0	1	3		3					1	0	0	0									1	1ADHD	1	0		
131	131Rg	7	M	1	2		1	1					3			1	0	0	0									1	1ADHD	1	1		
132	132Yuv	11	M	2	0		1	1	3		3					1	0	0	0						1				0	0	0	0	
133	133Rj	7	M	0	1	1	0	1			2					1	1	0		1		1						1	1ADHD	1	0		
134	134Ma	3	M	0	2		0	0	0							0	0	1			1							1	0	1	0		1
135	135Bk	5	F	0	0	1	0	1					3			1	0	0				1		1				1	1hy	1	1		
136	136Tm	7	M	0	0		0	1							1	1	0	0					1					1	1ADHD	1	0		
137	137SR	4	M	0	2		0	1							1	1	0	0				1						1	0	1	1		
138	138Dl	1	F	0	2		0	0	0							0	0	1			1							1	1	1	0		1
139	139Si	6	M	1	0		1	1					3			0	0	0	0						1				1ADHD	1	0		
140	140Sy	8	M	0	0	1	0	1					3			1	0	0				1							1ADHD	1	0		
141	141M1n	2	M	0	0		0	0	0							0	0	1			1							1	0	1	0		1
142	142Pr	1.6	M	0	2		0	0					3			0	1	0			1							1	0	1	0		
143	143Tk	1.6	M	0	2		0	0					3			1	0	0	0									1	0	1	0		
144	144Tv	1	M	0	2	1	0	1							1	1	1	0	0									1	0	0	1	1	
145	145Su	2	M	2	0		0	0	0							0	1	0	0									1	0	1	1		
146	146Bra	3.6	M	1	1	1	0	1						3		1	0	0				1				1			0	0	1	0	
147	147MC	2	F	1	0		0	1	2							1	0	0	0									1	0	0	1		
148	148SM	5	M	1	0		0	1	2							1	0	0	0									1	1	1	1	0	
149	149KM	4.6	M	0	0	0	0	1			1				`													1	1	1	1		
150	150RI	1.6	F	0	0	0	0	1			1					1	1	0			1							1	1Stereo	1	1		
151	151Vls	10/12	M	0	0	0	0	1			1						0	0	1											1	1		
152	152vs	6/12	F					1			1																				1		

Risk Factors3	Risk Factors4	Risk Factors5	Risk Factors6	Risk Factors7		Risk Factors9	Risk Factors10	FebrileFactors11	Risk Factors12	Risk Factors13	Risk Factors14	H/o Status	Consanguinity/	Family History	Neuro exam 0	Neuro Exam1	Neuro Exam2	Neuro Exam3	Neuro Exam4	Neuro Exam5	Neuro Exam6	Neuro Exam7	Neuro Exam8	Neuro Exam9	CT Brain1	CT Brain7	CT Brain2	CT Brain3	CT Brain4	CT Brain5	CT Brain6	CT Brain8	CT Brain9
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Risk Factors3	Risk Factors4	Risk Factors5	Risk Factors6	Risk Factors7		Risk Factors9	Risk Factors10	FebrileFactors11	Risk Factors12	Risk Factors13	Risk Factors14	H/o Status	Consanguinity/	Family History	Neuro exam 0	Neuro Exam1	Neuro Exam2	Neuro Exam3	Neuro Exam4	Neuro Exam5	Neuro Exam6	Neuro Exam7	Neuro Exam8	Neuro Exam9	CT Brain1	CT Brain7	CT Brain2	CT Brain3	CT Brain4	CT Brain5	CT Brain6	CT Brain8	CT Brain9
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CT Brain10	MRI.0		MRI.1	MRI.2	MRI.3	MRI.4	MRI.5	MRI.6	MRI.8	MRI.9	MRI.10	MRI.11	MRI.12	EEG	TMS/ UMS	Karyo typing	No of AEDS.2	No of AEDS. 3	No of AEDS.4	No of AEDS.5	No of AEDS.6	Seizure score1	Seizure score2	Seizure score3	Seizure score4	Seizure score5	Seizure score6	Seizure score7	Seizure score8	Seizure score9	Seizure score10	Seizure score11	Miscel commen
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1		46	0										1	1	0			1										1					B-ICT
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		49	1	1						1				1	0			1								1							
		50	0					1						1	0			1												1			TS
1		51	0										1	0	0			1										1					Haem
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1		62	0										1	1	0				1								1						VKD
	1	63	0							1				1	0	0		1												1			GES
		64	0											1	0			1											1				HYPara
		65	1							1				1	0					1									1				NDD
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	1	67	1											0	0				1							1							
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	1	78	0											0	0	0		1								1							
		79	1											1	0				1											1			
		80	0							1				1	0				1								1						TORCH
		81	0						1					0	0	0			1										1				NMD
		82	0							1				0	1						1									1			IEE
	1	83	0											0	0				1											1			
	1	84	0											0	0	0	1										1						C LIMB A
	1	85	0											0	0			1														1	
		86	0							1				1	0		1									1							
		87	1										1	0	0			1														1	
		88	0							1				1	0					1										1			
	1	89	0											1	0		1										1						

CT Brain10	MRI.0		MRI.1	MRI.2	MRI.3	MRI.4	MRI.5	MRI.6	MRI.8	MRI.9	MRI.10	MRI.11	MRI.12	EEG	TMS/ UMS	Karyo typing	No of AEDS.2	No of AEDS. 3	No of AEDS.4	No of AEDS.5	No of AEDS.6	Seizure score1	Seizure score2	Seizure score3	Seizure score4	Seizure score5	Seizure score6	Seizure score7	Seizure score8	Seizure score9	Seizure score10	Seizure score11	Miscel commen
	1	90	0											1	0	0		1												1			
	1	91	0											1	1						1									1			
	1	92	0											1	0	0		1										1					
		93	0							1				1	0					1									1				
		94	0	1										1	0				1								1						
		95	1											1	0			1											1				hie
		96	0									1		1	0						1							1						mts
	1	97	0											1	0			1												1			cp
		98	0	1										1	0			1									1						1nf
		99	1											1	0			1												1			
		100	1											1	0			1											1				
	1	101	0											1	0			1											1				WEST
		102	1							1				1	0		1									1							
	1	103	0											1	0			1									1						
		104	1											1	0			1														1	HIE
		105	0							1				1	0			1											1				IF
	1	106	0											1	0				1									1					
		107	1	1						1				1	0		1													1			
		108	1	1						1				1	0		1									1							HIE
		109	0		1									1	1				1								1						DAN.W
		110	1							1				0	0					1									1				HIE
		111	1											1	0				1									1					
		112	1							1				1	0					1								1					HIE
		113	1											1	0				1							1							TRA
		114	0		1				1					1	0			1															
		115	0							1				1	0				1								1						
	1	116	0											1	0				1										1				Hyper
		117	0		1					1				1	0			1												1			dysm
		118	1	1										1	0		1											1				Cafe
	1	119	0							1				0	0	0		1								1							
		120	0	1										1	0			1										1					
	1	121	0											1	0		1									1							
	1	122	0											1	0			1										1					ADHD
	1	123	0											1	0			1									1						ADHD
	1	124	0											1	0		1										1						
	1	125	0											1	0			1									1						
	1	126	0											1	0			1								1							ADHD
		127	0	1						1				1	0			1										1					
		128	0							1				1	0			1										1					
	1	129	0											1	1						1											1	
	1	130	0											1	0			1								1							
		131	1											1	1						1									1			MELAS
	1	132	0											1	0		1									1							
		133	0							1				1	0					1									1				
		134	0					1						1	0			1													1		
		135	0							1				1	0				1									1					
		136	1											0	0				1									1					
		137	1											1	0					1									1				
		138	0					1						1	0				1												1		
		139	1											1	0			1										1					
		140	1											1	0				1										1				
		141	0					1						1	0			1													1		
		142	1							1				1	0			1									1						HIE
		143	1							1				1	0			1									1						HIE
	1	144	0											1	0	0		1								1							
		145	1											1	0			1												1			
	1	146	0											1	0			1									1						CPS
1		147	1										1	1	0				1								1						JE
		148	0									1		1	0			1									1						MTLS
			1							1				1				1									1						ADHD
			1											1				1									1						Srereo
			1							1				1				1									1						
			0										1					1												1			PZM